

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
24 June 2004 (24.06.2004)

PCT

(10) International Publication Number
WO 2004/053057 A2

(51) International Patent Classification⁷: C12N

(21) International Application Number:
PCT/US2003/034563

(22) International Filing Date: 31 October 2003 (31.10.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/432,651 11 December 2002 (11.12.2002) US

(71) Applicant: 3M INNOVATIVE PROPERTIES COMPANY [US/US]; 3M Center, Post Office Box 33427, Saint Paul, MN 55133-3427 (US).

(72) Inventors: GUPTA, Shalley K.,; Post Office Box 33427, Saint Paul, MN 55133-3427 (US). GHOSH, Tarun K.,; Post Office Box 33427, Saint Paul, MN 55133-3427 (US). FINK, Jason R.,; Post Office Box 33427, Saint Paul, MN 55133-3427 (US).

(74) Agents: GRAM, Christopher D., et al.; Office of Intellectual Property Counsel, Post Office Box 33427, Saint Paul, MN 55133-3427 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT (utility model), AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA,

CH, CN, CO, CR, CU, CZ (utility model), CZ, DE (utility model), DE, DK (utility model), DK, DM, DZ, EC, EE (utility model), EE, EG, ES, FI (utility model), FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK (utility model), SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for all designations
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations

Published:

- without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: GENE EXPRESSION SYSTEMS AND RECOMBINANT CELL LINES

(57) Abstract: The present invention provides gene expression systems useful for detecting agonists of Toll-like receptors. The gene expression systems include a nucleic acid sequence encoding a Toll-like receptor and a second nucleic acid sequence that encodes a reporter operably linked to an expression control sequence. The recombinant cell lines include a gene expression system according to the present invention.

WO 2004/053057 A2

GENE EXPRESSION SYSTEMS AND RECOMBINANT CELL LINES

Background of the Invention

Cells of the immune system secrete a diverse set of compounds including
5 cytokines, chemokines, co-stimulatory markers, and defensins in response to an immunological challenge.

Certain compounds known as immune response modifiers ("IRMs") possess potent immunostimulating activity including but not limited to antiviral and antitumor activity. Certain IRMs effect their immunostimulatory activity by, e.g., inducing the production and
10 secretion of certain cytokines while inhibiting production and secretion of other cytokines. Certain IRMs are small organic molecules such as those disclosed in, for example, U.S. Patent Nos. 4,689,338; 4,929,624; 5,266,575; 5,268,376; 5,352,784; 5,389,640; 5,482,936; 5,494,916; 6,110,929; 6,194,425; 4,988,815; 5,175,296; 5,367,076; 5,395,937; 5,693,811; 5,741,908; 5,238,944; 5,939,090; 6,245,776; 6,039,969; 6,083,969; 6,245,776; 6,331,539;
15 and 6,376,669; and PCT Publications WO 00/76505; WO 00/76518; WO 02/46188, WO 02/46189; WO 02/46190; WO 02/46191; WO 02/46192; WO 02/46193; and WO 02/46194.

Additional small molecule IRMs include purine derivatives (such as those described in U.S. Patent Nos. 6,376,50 and 6,028,076), small heterocyclic compounds
20 (such as those described in U.S. Patent No. 6,329,381), and amide derivatives (such as those described in U.S. Patent No. 6,069,149).

Other IRMs include large biological molecules such as oligonucleotide sequences. Some IRM oligonucleotide sequences contain cytosine-guanine dinucleotides (CpG) and are described, for example, in U.S. Patent Nos. 6,1994,388; 6,207,646; 6,239,116;
25 6,339,068; and 6,406,705. Other IRM nucleotide sequences lack CpG and are described, for example, in International Patent Publication No. WO 00/75304.

Some of these IRMs induce cellular responses (e.g., the production and/or secretion of cytokines, chemokines, etc.) through one or more Toll-like receptors (TLRs). For example, certain small organic molecule IRMs are agonists of one or more of TLR-1,
30 TLR-2, TLR-4, TLR-6, TLR-7, and TLR-8. Additionally, CpG has been reported to act through TLR 9.

In certain cells of the immune system, TLR activation can be associated with activation of the transcription factor NF- κ B. NF- κ B activation is associated with certain cellular responses to an immunological challenge, such as the production and secretion of pro-inflammatory cytokines such as TNF- α , IL-1, IL-6, IL-8, IL-10, IL-12, MIP-1, and MCP-1. IRM induction of such cellular responses can be demonstrated by measuring activation of the transcription factor NF- κ B in response to exposing a cell to an IRM compound (See, e.g., Chuang *et al.*, *Journ. of Leuk. Biol.*, vol. 71, pp. 538-544 (2002), and Hemmi *et al.*, *Nature Immunology*, vol. 3(2), pp. 196-200 (2002)). Thus, NF- κ B activation can be used as a reporter of TLR activation. However, the extent of NF- κ B activation does not necessarily correlate with the extent of the downstream cellular response. This is so because the downstream cellular response may be modulated by one or more additional factors.

Summary of the Invention

The present invention provides an expression system that includes a first nucleic acid sequence that encodes a Toll-like receptor operably linked to a first expression control sequence; and a second nucleic acid sequence that encodes a reporter that (a) generates a detectable signal when the reporter is expressed and the cell is exposed to conditions effective for generating the detectable signal, and (b) is operably linked to a second expression control sequence that comprises a cytokine promoter, a chemokine promoter, a co-stimulatory marker promoter, or a defensin promoter. In some embodiments, the first nucleic acid sequence and the second nucleic acid sequence are included on a single vector. In other embodiments, the first nucleic acid sequence and the second nucleic acid sequence are located on separate vectors.

In another aspect, the present invention provides a recombinant cell line that includes a host cell transfected with an expression system. In some embodiments, the expression system is contained within a single vector. In other embodiments, the expression system is contained among two or more vectors so that the host cell is co-transfected with all of the vectors of the expression system to obtain the recombinant cell line. In one embodiment, the host cell is a Namalwa cell.

In another aspect, the present invention provides a TLR agonist identified using either an expression system or a recombinant cell line according to the present invention.

In yet another aspect, the present invention provides pharmaceutical compositions including a TLR agonist identified using either an expression system or a recombinant cell line according to the present invention.

5 Various other features and advantages of the present invention should become readily apparent with reference to the following detailed description, examples, and appended claims. In several places throughout the specification, guidance is provided through lists of examples. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.

10 **Detailed Description of Illustrative Embodiments of the Invention**

The present invention provides gene expression systems and recombinant cell lines that may be useful for detecting TLR activation based on detecting induction of a downstream cellular response to TLR activation (e.g., production or secretion of one or more immune system compounds such as cytokines or co-stimulatory markers) rather than
15 NF- κ B activation. In some cases, the cellular response may be mediated by NF- κ B, but in other cases the cellular response may be NF- κ B-independent. Thus, the present invention provides gene expression systems and recombinant cell lines that may be useful for detecting a broader range of TLR activation than is possible by monitoring NF- κ B activation. This may provide an ability to identify certain TLR agonists that would not be
20 detected using an assay based on NF- κ B activation. The gene expression systems and recombinant cell lines of the present invention also may provide a more relevant indication of the quantitative character of a particular cellular response to TLR activation by a particular TLR agonist.

In some cases, a gene expression system or recombinant cell line according to the
25 present invention may be useful for detecting TLR activation that is not accompanied by NF- κ B activation. Accordingly, the gene expression system and recombinant cell line may be employed to identify TLR agonists that do not necessarily also activate NF- κ B. Such TLR agonists may be useful for treatment or prevention of certain conditions in which the production and secretion of pro-inflammatory cytokines such as those induced
30 by NF- κ B activation may be undesirable.

For purposes of this invention, the following terms shall have the meanings set forth.

“Activation” refers to modifying the indicated protein so that the protein provides a biological function. For example, TLR activation refers to modifying a TLR - for example, a conformational modification such as in response to exposure of the TLR to an agonist - so that the TLR is capable of inducing the production and secretion of certain cytokines.

“Agonist” refers to a compound that can combine with a receptor (e.g., a TLR) to produce a cellular response. An agonist may be a ligand that directly binds to the receptor. Alternatively, an agonist may combine with a receptor indirectly by, e.g., (a) forming a complex with another molecule that directly binds to the receptor, or (b) otherwise results in the modification of another compound so that the other compound directly binds to the receptor. An agonist may be referred to as an agonist of a particular TLR (e.g., a TLR6 agonist).

“Amino acid sequence” refers to a particular ordered sequence of amino acids, whether naturally occurring or engineered.

“Co-transfect” and variations thereof refer to transfecting a host cell with more than one vector. A host cell may be co-transfected by transfecting with two or more vectors one at a time or in any convenient combination of vectors, including simultaneous transfection with all vectors.

“Express” and variations thereof refer to the ability of a cell to transcribe a structural gene to mRNA, then translate the mRNA to synthesize a protein that provides a detectable biological or biochemical function. “Expressible” refers to the ability of a particular nucleic acid sequence to be expressed by a cell that contains the nucleic acid sequence.

“Immune system compound” refers to any compound that is produced or secreted by cells of the immune system in response to an immunological challenge. Immune system compounds include but are not limited to cytokines, chemokines, co-stimulatory markers, and defensins.

“IRM compound” refers to a compound that alters the level of one or more immune system compounds when administered to an IRM-responsive cell. Representative IRM compounds include the small organic molecules, purine derivatives, small heterocyclic compounds, amide derivatives, and oligonucleotide sequences described above.

“Nucleic acid sequence” refers generally to a region of DNA that has a definable function such as (a) encoding a peptide, polypeptide, or protein or (b) controlling expression of a nucleic acid sequence that encodes a peptide, polypeptide, or protein. For example, a nucleic acid sequence that encodes TLR6 refers generically to any sequence of
5 nucleotides that encodes a TLR6 protein, without regard to (a) the species source of the nucleic acid sequence, (b) specific nucleotide sequence variants, or (c) whether such nucleotide sequence variants are naturally occurring or engineered.

“Nucleotide sequence” refers to a particular ordered sequence of nucleotide bases, whether naturally occurring or engineered.

10 It has been found that induction of certain secreted proteins or polypeptides can be useful as reporters of TLR activation. For example, IFN- α is a cytokine secreted by such immune system cells as T lymphocytes, macrophages, plasmacytoid monocytes, dendritic cells, and natural killer cells. IFN- α is involved in regulating a host’s innate and adaptive immune responses to an immunological challenge, perhaps by providing a link between
15 the two responses [Brassard *et al.*, *Journal of Leukocyte Biology* 71: 565-581 (2002)]. The innate immune response can include the cell-mediated response of natural killer (NK) cells to a non-self (e.g., neoplastic) or foreign (e.g., viral) antigen. IFN- α also may indirectly regulate the balance between Th1 and Th2 cell populations and, therefore, the innate and adaptive immune responses. Moreover, induction of IFN- α is independent of NF- κ B
20 activation.

Additionally, the production and secretion of NF- κ B-dependent cytokines can be useful as reporters of cellular responses resulting from immunological challenge. Detection and measurement of such cytokines may provide comparative qualitative data regarding a cell’s response to immunological challenge that is more relevant to an
25 investigator than NF- κ B activation data.

Thus, in certain embodiments, the present invention relates to recombinant cell lines and gene expression systems designed to assist detecting induction of immune system compounds and identification of compounds that induce expression of immune system compounds through TLRs.

30 Parts of the following description are provided in the context of IFN- α induction and detection. However, many of the features of the embodiments described below also may be realized using expression systems and recombinant cell lines designed to

specifically detect or induce other immune system compounds. Thus, expression systems and recombinant cell lines designed to specifically detect or induce immune system compounds other than IFN- α are explicitly included in the scope of the present invention.

5 The present invention provides a recombinant cell line capable of inducing gene expression from an expression control sequence of a gene that encodes an immune system compound (e.g., IFN- α) in response to TLR activation. In some embodiments, for example, cells of the recombinant cell line, when exposed to a TLR agonist, can induce expression from an IFN- α promoter to a greater extent than cells of the corresponding untransfected cell line. Cells of the untransfected cell lines may substantially lack a
10 functional level of TLR expression (i.e., untransfected cells may not detectably induce expression from the IFN- α promoter in response to exposure to a TLR agonist). Alternatively, cells of the untransfected cell line may exhibit a baseline level of background TLR function, but the baseline level is less than the level of TLR function observed in cells of the corresponding recombinant (i.e., transfected) cell line.

15 Cells of the recombinant cell lines include a first nucleic acid sequence that encodes a TLR operably linked to an expression control sequence. The cells also include a second nucleic acid sequence that encodes a reporter capable of generating a detectable signal when it is expressed in the recombinant cell under conditions suitable for generating the detectable signal. The reporter is linked to a second expression control sequence that
20 is capable of being induced by activation of the TLR encoded by the first nucleic acid sequence.

The TLR encoded by the first nucleic acid sequence may be any TLR. Ten different human TLRs have been identified, cloned, and sequenced. TLRs also are known to exist in other mammals including, for example, mice and chimpanzees. The nucleotide
25 sequences of the ten human TLRs and many non-human TLRs are known, have been published, and are readily accessible from various sequence databases including GenBank. The first nucleic acid sequence may include the nucleotide sequence of any one of the TLRs, whether human or non-human. In one embodiment, the TLR is human TLR6; in another embodiment, the TLR is human TLR7. Alternatively, the first nucleic acid may
30 encode any one of the ten human TLRs, any non-human TLR, or any combination of two or more TLRs that may be desirable for a particular construct.

The first nucleic acid sequence can include a nucleotide sequence that differs from a specific published nucleotide sequence for the TLR encoded by the first nucleic acid sequence. For example, the first nucleic acid sequence can contain one or more substitutions (compared to a published TLR nucleotide sequence) that do not alter the amino acid sequence of the TLR protein expressed from the first nucleic acid sequence. Such a substitution may be termed a degenerate substitution. Nucleotide sequences containing one or more degenerate substitutions compared to a known TLR nucleotide sequence are explicitly included within the scope of nucleotide sequences suitable for use within the first nucleic acid sequence.

As another example, certain nucleotide substitutions may alter the amino acid sequence of the TLR protein. For certain amino acid substitutions, however, the chemical properties of the protein having the altered amino acid sequence are similar to the chemical properties of the protein having the native amino acid sequence. Amino acids may be divided into four groups based on the chemical characteristics of the amino acid side groups: neutral, non-polar amino acids include glycine, alanine, valine, isoleucine, leucine, phenylalanine, proline, and methionine; neutral, polar amino acids include serine, threonine, tyrosine, tryptophan, asparagine, glutamine, and cysteine; acidic amino acids include aspartic acid and glutamic acid; and basic amino acids include lysine, arginine, and histidine. Substitution of one amino acid for another amino acid within the same group may have little or no functional effect on the resulting protein because of the similarity of the chemical characteristics of the amino acids involved in the substitution. Such amino acid substitutions may be termed a conservative amino acid substitution. Nucleotide sequences that, when compared to a known TLR nucleotide sequence, generate one or more conservative amino acid substitutions are explicitly included within the scope of nucleotide sequences suitable for use within the first nucleic acid sequence.

The nucleic acid that encodes a TLR may be cloned into an expression vector so that it is under the expression control of its own promoter, a homologous TLR promoter, or any heterologous promoter inducible in an appropriate host cell. For example, in certain embodiments, the TLR6 structural gene may be cloned into the commercially available mammalian expression vector pCI-neo. In this case, the TLR6 structural gene may be cloned into the vector's cloning region using the NheI and MluI restrictions sites. In such an embodiment, after transfection of the vector into a mammalian cell, the TLR6

structural gene is under the transcriptional control of the vector's CMV enhancer/promoter region.

5 The second nucleic acid sequence encodes a reporter that is capable of generating a detectable signal when expressed in a host cell under conditions appropriate for generating the desired detectable signal. A wide variety of suitable reporter systems are known. For example, luciferase gene expression may generate a detectable luminescent signal under appropriate conditions. As another example, β -galactosidase expression can generate a detectable color change under appropriate conditions. As yet another example, production and secretion of an immune system compound may be detected by an enzyme-linked immunosorbent assay (ELISA). These and other reporter systems are known and
10 assays for generating the detectable signals are commercially available.

The second nucleic acid sequence is operably linked to a second expression control sequence that includes a promoter sequence selected to be inducible by activation of the TLR encoded by the first nucleic acid sequence. Thus, expression and activation of the
15 TLR encoded by the first nucleic acid sequence will induce gene expression from the second expression control sequence, thereby causing expression of the reporter, which may be detected by performing an assay designed to detect expression of the reporter. The second expression control sequence may include any suitable nucleotide sequence that can induce expression (e.g., a promoter) of a structural gene upon activation of the TLR
20 encoded by the first nucleic acid sequence. Nucleotide sequences suitable for use as second expression control sequences include promoter sequences of TLR-inducible genes including but not limited to genes encoding cytokines, chemokines, co-stimulatory markers, and defensins. In certain embodiments, the second expression control sequence can include an IFN- α 1 promoter. When the reporter system being employed to detect
25 TLR activation includes detecting production and secretion of an immune system compound with an appropriate ELISA assay, the second expression control sequence may include the promoter of the gene encoding the immune system compounds being expressed and detected as the reporter. However, in certain embodiments, it may be desirable to express the immune system compound from a heterologous promoter.

30 The first nucleic acid sequence and the second nucleic acid sequence may be contained within a single vector. Alternatively, the first nucleic acid sequence and the second nucleic acid sequence may be on separate vectors and co-transfected into a suitable

host cell. In certain embodiments, for example, the first nucleic acid sequence may be cloned into the pCI-neo vector as described above, while the second nucleic acid sequence can be cloned into a reporter vector. One example of a commercially available reporter vector is the pGL3-Enhancer vector, which includes a luciferase reporter gene downstream of a cloning site for cloning a promoter sequence of interest. In some embodiments, the promoter of a TLR-inducible immune system compound may be cloned into the pGL3-Enhancer cloning site. In one such embodiment, the IFN- α promoter may be cloned into the pGL3-Enhancer cloning site.

Suitable host cells include any transfectable cells capable of expressing exogenous mammalian genes. In some embodiments, the host cells may be mammalian cells such as human cells or mouse cells. For example, suitable host cells include human cells or descendants of a human cell including but not limited to Namalwa cells or HEK293 cells. Alternatively, the host cells may be mouse cells or descendants of a mouse cell including but not limited to RAW 264.7 cells.

In one embodiment, the host cells include Namalwa cells. Namalwa cells have certain characteristics that may be particularly desirable for certain embodiments of the present invention. For example, Namalwa cells can include an expressible chromosomal IFN- α gene locus. Thus, upon appropriate stimulation (e.g., viral infection), Namalwa cells can be induced to produce and secrete IFN- α from the chromosomal IFN- α gene locus. However, Namalwa cells do not naturally express certain TLRs (e.g., TLR6, TLR7, or TLR9). Certain agonists of such TLRs have been shown to induce IFN- α expression in other cell types (e.g., PMBCs), but may not induce IFN- α expression in Namalwa cells unless a functional level of TLR expression is provided.

Namalwa cells transfected with an expression system according to the present invention may be capable of expressing a functional level of the TLR provided by the expression system. Thus, Namalwa cells transfected with an expression system according to certain embodiments of the present invention may inducibly express IFN- α as a result of activating the cloned TLR (e.g., by exposure of the transfected Namalwa cells to an agonist). Thus, certain transfected cell lines of the present invention provide an ability to detect a TLR agonist by detecting TLR-mediated IFN- α expression by Namalwa cells. Such IFN- α expression may occur from the chromosomal IFN- α gene or from an IFN- α promoter cloned into the reporter vector.

Namalwa cells transfected with an expression system according to certain embodiments of the present invention can provide alternative means of detecting TLR expression. First, transfected Namalwa cells may generate a detectable signal as a result of expressing the reporter from the second expression control sequence, which may or may not include an IFN- α promoter (see Table 2). Second, transfected Namalwa cells may produce and secrete IFN- α from the chromosomal IFN- α gene locus. A transfected Namalwa cell line according to the present invention may be used to screen compounds in order to identify those compounds that induce TLR expression, i.e., TLR agonists.

Therefore, the present invention also provides TLR agonist compounds identified using an expression system or a recombinant cell line according to certain embodiments of the present invention. As described above, the expression systems and recombinant cell lines may provide the ability to identify TLR activation that may not be detectable using previously known TLR activation assays. A compound that induces TLR activity detectable by using a gene expression system or a recombinant cell line according to the present invention may be considered a TLR agonist. Such TLR agonists may include chemical structures similar in certain respects to the chemical structures of known IRM compounds. Alternatively, a gene expression system or a recombinant cell line according to the present invention may provide a tool for the screening (e.g., high throughput screening) chemically diverse compounds that may lead to the discovery of new TLR agonists, some of which may contain new chemical core structures capable of activating TLRs.

The present invention also provides pharmaceutical compositions containing a TLR agonist identified using an expression system or a recombinant cell line according to the present invention, or a pharmaceutically acceptable salt thereof, in an amount effective for inducing a TLR-mediated cellular response.

Examples

The following examples have been selected merely to further illustrate features, advantages, and other details of the invention. It is to be expressly understood, however, that while the examples serve this purpose, the particular materials and amounts used as well as other conditions and details are not to be construed in a manner that would unduly limit the scope of this invention.

Construction of vectors

The vector pIFN- α 1-luc was constructed by inserting BglII sites at both ends of the human IFN- α 1 promoter (SEQ ID NO:21). The BglII sites were inserted into the IFN- α 1 promoter and the sequence was amplified using the primer pair of SEQ ID NO:22 and SEQ ID NO:23. The amplified IFN- α 1 promoter was cloned into the pGL3-Enhancing vector (Promega Corp., Madison, WI) at its BglII site.

The vector pCI-TLR6 was constructed by inserting SEQ ID NO:11 (GenBank Accession No. NM 006068), which includes the human TLR6 coding sequence, into the pCI-neo mammalian expression vector (Promega Corp.) at the vector's NheI and MluI restriction sites.

Transfections

Unless otherwise indicated, all incubations were performed at 37°C with 5% CO₂ at 98% humidity.

Culture medium was prepared from complete RPMI 1640 medium (BioSource International, Inc., Camarillo, CA). Fetal bovine serum (Atlas Biologicals, Inc., Ft. Collins, CO) was added to a final concentration of 7.5% (vol/vol); L-glutamine (BioSource International, Inc.) was added to 5 mM; and sodium pyruvate (BioSource International, Inc.) was added to 1 mM.

Burkitt's Lymphoma lymphoblastoid Namalwa cells (ATCC Accession No. CRL-1432) were grown by incubation in culture medium overnight. Cells were harvested by centrifugation in a tabletop centrifuge (1200 RPM for 5 minutes), and then resuspended in phosphate buffered sucrose to a concentration of 1.3×10^7 cells per milliliter.

For each transfection, a 750 μ L aliquot of the cell suspension was placed in an electroporation cuvette with 4 mm gaps. 10 μ g of the pIFN- α 1-luc vector and 10 μ g of the pCI-TLR6 vector were added to the electroporation cuvette. The cell and vector mixtures were incubated at room temperature for 5 minutes. The cells were electroporated using a BioRad Gene Pulser (BioRad Laboratories, Hercules, CA) set to at 500 μ F capacitance and 0.27 volts, then incubated at room temperature for 5 minutes.

The electroporated cells were suspended in 10 mLs of culture medium and incubated overnight. Dead cells and debris were removed after 24 hours using a MACS

Dead Cell Removal kit (Miltenyi Biotec, Auburn, CA). Cells were resuspended in 10 mLs of culture medium and incubated for an additional 24 hours.

Transfected cells were selected by adding G418 (Promega Corp., Madison, WI) to a final concentration of 1 mg/mL and incubating the cells for seven days.

5

Assays

The selected transfected cells were counted and resuspended to a concentration of 1×10^6 cell per mL in culture medium. 100 μ L aliquots of cells were placed in the wells of a white-walled, white-bottomed 96-well plate (Corning, Inc. Corning, NY). 1.0 μ L of an IRM compound from Table 1 (prepared at 1 mM in 100% DMSO) was added to some cell aliquots so that the final concentration of IRM compound was 10 μ M. As a positive control, some cell aliquots were incubated with Sendai virus instead of IRM compound. As a negative control, some cell aliquots were incubated with DMSO without IRM compound. In all cases, the cells were incubated for 18 hours.

15

Table 1 - IRM Compounds

Compound	Chemical Name	Citation
IRM 1	4-amino-2-ethoxymethyl- α,α -dimethyl-6,7,8,9-tetrahydro-1 <i>H</i> -imidazo[4,5- <i>c</i>]quinoline-1-ethanol	U.S. 5,352,784 Example 91
IRM 2	4-amino- $\alpha,\alpha,2$ -trimethyl-1 <i>H</i> -imidazo[4,5- <i>c</i>]quinoline-1-ethanol	U.S. 5,266,575 Example C1
IRM 3	N-[4-(4-amino-2-butyl-1 <i>H</i> -imidazo[4,5- <i>c</i>]quinolin-1-yl)butyl]methanesulfonamide	U.S. 6,331,539 Example 6
IRM 4	1-{2-[3-(3-pyridyl)propoxy]ethyl}-1 <i>H</i> -imidazo[4,5- <i>c</i>]quinolin-4-amine	WO 02/46193 Example 33
IRM 5	2-butyl-1-(2-methylpropyl)-1 <i>H</i> -imidazo[4,5- <i>c</i>][1,5]naphthyridin-4-amine	U.S. 6,194,425 Example 39
IRM 6	2-butyl-6,7,8,9-tetrahydro-1-(2-methylpropyl)-1 <i>H</i> -imidazo[4,5- <i>c</i>][1,5]naphthyridin-4-amine	U.S. 6,194,425 Example 40
IRM 7	N ³ -{4-[4-amino-2-(2-methoxyethyl)-1 <i>H</i> -imidazo[4,5- <i>c</i>]quinolin-1-yl]butyl}-6-(1 <i>H</i> -1-pyrrolyl)nicotinamide	U.S. 6,451,810 Example 60
IRM 8	2-ethyl-1-[5-(methylsulfonyl)pentyl]-1 <i>H</i> -imidazo[4,5- <i>c</i>]quinolin-4-amine	WO 02/46192 Example 13

The plates were equilibrated to room temperature before 1 volume of reconstituted LucLight Plus (Packard Instruments, Meriden, CT) was added to each aliquot of cells. Each well of the plate was read on an LJI Analyst (LJI Biosystems, Inc., Sunnyvale, CA) set with a 5 minute dark adapt. Data from a representative experiment are shown in Table 2. The data are expressed as the fold increase in luciferase induction off of the IFN- α 1 promoter in cell aliquots incubated with the indicated stimulant compared to the negative control in which the cell aliquots were incubated with only DMSO.

Table 2 - TLR Expression by pIFN- α 1-luc/pCI-TLR6 Co-Transfected Namalwa cells

<u>Stimulant</u>	<u>Fold Increase in Luciferase Induction</u>
IRM1	3.6
IRM2	2.7
IRM3	2.6
IRM4	4.0
IRM5	3.2
IRM6	2.9
IRM7	3.2
IRM8	2.3
Sendai virus	2.7

The complete disclosures of the patents, patent documents and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. In case of conflict, the present specification, including definitions, shall control.

Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. Illustrative embodiments and examples are provided as examples only and are not intended to limit the scope of the present invention. The scope of the invention is limited only by the claims set forth as follows.

What is Claimed is:

1. An expression system comprising:
a first nucleic acid sequence that encodes a Toll-like receptor operably linked to a first expression control sequence; and
5 a second nucleic acid sequence that encodes a reporter that (a) generates a detectable signal when the reporter is expressed and the cell is exposed to conditions effective for generating the detectable signal, and (b) is operably linked to a second expression control sequence that comprises a cytokine promoter, a chemokine promoter, a co-stimulatory marker promoter, or a defensin promoter.
10
2. The expression system of claim 1 wherein the second expression control sequence comprises an IFN- α promoter.
3. The expression system of claim 1 wherein the first nucleic acid sequence
15 comprises the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, or a degenerate variant of any of the foregoing.
4. The expression system of claim 1 wherein the first nucleic acid sequence
20 comprises a nucleotide sequence that encodes a polypeptide having the sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, or any one of the foregoing sequences with one or more conservative amino acid substitutions.
- 25 5. The expression system of claim 1 wherein the detectable signal comprises luciferase activity or β -galactosidase activity.
6. The expression system of claim 1 wherein a first vector comprises the first nucleic acid sequence and a second vector comprises the second nucleic acid sequence.
30
7. A vector comprising the expression system of claim 1.

8. A TLR agonist identified using the expression system of claim 1.
9. A pharmaceutical composition comprising the TLR agonist of claim 8, or a pharmaceutically acceptable salt thereof.
- 5 10. A cultured cell comprising the expression system of claim 1.
11. The cultured cell of claim 10 wherein the cell is a mammalian cell or a descendent of a mammalian cell.
- 10 12. The culture cell of claim 11 wherein the cell is a human cell or a descendent of a human cell.
13. The cultured cell of claim 10 further comprising an expressible nucleic acid
15 sequence that encodes IFN- α operably linked to a third expression control sequence.
14. The cultured cell of claim 13 wherein the expressible nucleic acid sequence that encodes IFN- α is located on a chromosome of the cultured cell.
- 20 15. The cultured cell of claim 14 wherein the cultured cell is a Namalwa cell.
16. The cultured cell of claim 13 wherein the expressible nucleic acid sequence that encodes IFN- α is located on an extrachromosomal vector.
- 25 17. A TLR agonist identified using the cultured cell of claim 10.
18. A pharmaceutical composition comprising the TLR agonist of claim 17, or a pharmaceutically acceptable salt thereof.

30

58182US002.ST25.txt
SEQUENCE LISTING

<110> Gupta, Shalley K.
Ghosh, Tarun K.
Fink, Jason R.

<120> Gene Expression Systems and Recombinant Cell Lines

<130> 58182WO003

<160> 23

<170> PatentIn version 3.1

<210> 1

<211> 2832

<212> DNA

<213> Homo sapiens

<400> 1

```
acagactgcc aaatggaaca gacaagcagg ttgtcttggtg ttaaagaaaa tgagatatga      60
gtcagttact cccggaggca atgctgctgt tcagctcttg tgtttttggtg gccaggggtct      120
tcatgaacac taataggggt accaggccct cttccttggtt agaagaaatc aggataacaa      180
aggtatatgt ggcaccccta caaaaggaat ctgtatctgt atcaagatga tctgaagaac      240
agcttctacc tttaggaatg tctagtgttc caaaatgact agcatcttcc attttgccat      300
tatcttcatg ttaatacttc agatcagaat acaattatct gaagaaagtg aatttttagt      360
tgataggtca aaaaacggtc tcatccacgt tcctaaagac ctatcccaga aaacaacaat      420
cttaaataata tcgcaaaatt atatatctga gctttggact tctgacatct tatcactgtc      480
aaaactgagg attttgataa tttctcataa tagaatccag tatcttgata tcagtgtttt      540
caaattcaac caggaattgg aatacttgga tttgtccac aacaagttgg tgaagatttc      600
ttgccaccct actgtgaacc tcaagcactt ggacctgtca tttaatgcat ttgatgccct      660
gcctatatgc aaagagtttg gcaatatgtc tcaactaaaa tttctgggggt tgagcaccac      720
acacttagaa aaatctagtg tgctgccaat tgctcatttg aatatcagca aggtcttgct      780
ggctcttaga gagacttatg gggaaaaaga agaccctgag ggccttcaag actttaacac      840
tgagagtctg cacattgtgt tccccacaaa caaagaattc cattttatatt tggatgtgtc      900
agtcaagact gtagcaaatc tggaactatc taatatcaaa tgtgtgctag aagataacaa      960
atgttcttac ttcctaagta ttctggcgaa acttcaaaca aatccaaagt tatcaagtct     1020
taccttaaac aacattgaaa caacttgga ttttttcatt aggatcctcc agctggtttg     1080
gcatacaact gtatgggtatt tctcaatttc aaacgtgaag ctacagggtc agctggactt     1140
cagagatfff gattattctg gcacttcctt gaaggccttg tctatacacc aagttgtcag     1200
cgatgtgttc ggttttccgc aaagttatat ctatgaaatc ttttcgaata tgaacatcaa     1260
aaatttcaca gtgtctggta cacgcatggt ccacatgctt tgcccatcca aaattagccc     1320
```

58182US002.ST25.txt

```

gttcctgcat ttggattttt ccaataatct cttaacagac acggtttttg aaaattgtgg 1380
gcaccttact gagttggaga cacttatttt acaaatgaat caattaaaag aactttcaaa 1440
aatagctgaa atgactacac agatgaagtc tctgcaacaa ttggatatta gccagaattc 1500
tgtaagctat gatgaaaaga aaggagactg ttcttggact aaaagtttat taagtttaaa 1560
tatgtcttca aatatactta ctgacactat tttcagatgt ttacctcca ggatcaaggt 1620
acttgatctt cacagcaata aaataaagag cattcctaaa caagtcgtaa aactggaagc 1680
tttgcaagaa ctcaatgttg ctttcaattc ttttaactgac cttcctggat gtggcagctt 1740
tagcagcctt tctgtattga tcattgatca caattcagtt tcccacccat cagctgattt 1800
cttcagagc tgccagaaga tgaggatcaat aaaagcaggg gacaatccat tccaatgtac 1860
ctgtgagcta ggagaatttg tcaaaaatat agaccaagta tcaagtgaag tgtagaggg 1920
ctggcctgat tcttataagt gtgactacc ggaaagttat agaggaaccc tactaaagga 1980
ctttcacatg tctgaattat cctgcaacat aactctgctg atcgtcacca tcgttgccac 2040
catgctggtg ttggctgtga ctgtgacctc cctctgcac tacttggtac tgccctggta 2100
tctcaggatg gtgtgccagt ggaccagac ccggcgcagg gccaggaaca tacccttaga 2160
agaactccaa agaaatctcc agtttcatgc atttatttca tatagtgggc acgattcttt 2220
ctgggtgaag aatgaattat tgccaaacct agagaaagaa ggtatgcaga tttgccttca 2280
tgagagaaac tttgttcctg gcaagagcat tgtggaaaat atcatcacct gcattgagaa 2340
gagttacaag tccatctttg ttttgtctcc caactttgtc cagagtgaat ggtgccatta 2400
tgaactctac tttgcccac acaatctctt tcatgaagga tctaatagct taatcctgat 2460
cttgctggaa ccattccgc agtactccat tcctagcagt tatcacaagc tcaaaagtct 2520
catggccagg aggacttatt tggaatggcc caaggaaaag agcaaactg gccttttttg 2580
ggctaactta agggcagcca ttaatattaa gctgacagag caagcaaaga aatagattac 2640
acatcaagtg aaaaatattc ctctgttga tattgctgct tttggaagtt ccaacaatga 2700
ctttattttg catcagcata gatgtaaaca caattgtgag tgtatgatgt aggtaaaaat 2760
atataccttc gggtcgcagt tcaccattta tatgtggtat taaaaattaa tgaaatgata 2820
taactttgat tt 2832

```

<210> 2
 <211> 786
 <212> PRT
 <213> Homo sapiens

<400> 2

Met Thr Ser Ile Phe His Phe Ala Ile Ile Phe Met Leu Ile Leu Gln
 1 5 10 15

58182US002.ST25.txt

Ile Arg Ile Gln Leu Ser Glu Glu Ser Glu Phe Leu Val Asp Arg Ser
20 25 30

Lys Asn Gly Leu Ile His Val Pro Lys Asp Leu Ser Gln Lys Thr Thr
35 40 45

Ile Leu Asn Ile Ser Gln Asn Tyr Ile Ser Glu Leu Trp Thr Ser Asp
50 55 60

Ile Leu Ser Leu Ser Lys Leu Arg Ile Leu Ile Ile Ser His Asn Arg
65 70 75 80

Ile Gln Tyr Leu Asp Ile Ser Val Phe Lys Phe Asn Gln Glu Leu Glu
85 90 95

Tyr Leu Asp Leu Ser His Asn Lys Leu Val Lys Ile Ser Cys His Pro
100 105 110

Thr Val Asn Leu Lys His Leu Asp Leu Ser Phe Asn Ala Phe Asp Ala
115 120 125

Leu Pro Ile Cys Lys Glu Phe Gly Asn Met Ser Gln Leu Lys Phe Leu
130 135 140

Gly Leu Ser Thr Thr His Leu Glu Lys Ser Ser Val Leu Pro Ile Ala
145 150 155 160

His Leu Asn Ile Ser Lys Val Leu Leu Val Leu Gly Glu Thr Tyr Gly
165 170 175

Glu Lys Glu Asp Pro Glu Gly Leu Gln Asp Phe Asn Thr Glu Ser Leu
180 185 190

His Ile Val Phe Pro Thr Asn Lys Glu Phe His Phe Ile Leu Asp Val
195 200 205

Ser Val Lys Thr Val Ala Asn Leu Glu Leu Ser Asn Ile Lys Cys Val
210 215 220

Leu Glu Asp Asn Lys Cys Ser Tyr Phe Leu Ser Ile Leu Ala Lys Leu
225 230 235 240

Gln Thr Asn Pro Lys Leu Ser Ser Leu Thr Leu Asn Asn Ile Glu Thr
245 250 255

Thr Trp Asn Ser Phe Ile Arg Ile Leu Gln Leu Val Trp His Thr Thr

58182US002.ST25.txt
265 270

260

Val Trp Tyr Phe Ser Ile Ser Asn Val Lys Leu Gln Gly Gln Leu Asp
275 280 285

Phe Arg Asp Phe Asp Tyr Ser Gly Thr Ser Leu Lys Ala Leu Ser Ile
290 295 300

His Gln Val Val Ser Asp Val Phe Gly Phe Pro Gln Ser Tyr Ile Tyr
305 310 315 320

Glu Ile Phe Ser Asn Met Asn Ile Lys Asn Phe Thr Val Ser Gly Thr
325 330 335

Arg Met Val His Met Leu Cys Pro Ser Lys Ile Ser Pro Phe Leu His
340 345 350

Leu Asp Phe Ser Asn Asn Leu Leu Thr Asp Thr Val Phe Glu Asn Cys
355 360 365

Gly His Leu Thr Glu Leu Glu Thr Leu Ile Leu Gln Met Asn Gln Leu
370 375 380

Lys Glu Leu Ser Lys Ile Ala Glu Met Thr Thr Gln Met Lys Ser Leu
385 390 395 400

Gln Gln Leu Asp Ile Ser Gln Asn Ser Val Ser Tyr Asp Glu Lys Lys
405 410 415

Gly Asp Cys Ser Trp Thr Lys Ser Leu Leu Ser Leu Asn Met Ser Ser
420 425 430

Asn Ile Leu Thr Asp Thr Ile Phe Arg Cys Leu Pro Pro Arg Ile Lys
435 440 445

Val Leu Asp Leu His Ser Asn Lys Ile Lys Ser Ile Pro Lys Gln Val
450 455 460

Val Lys Leu Glu Ala Leu Gln Glu Leu Asn Val Ala Phe Asn Ser Leu
465 470 475 480

Thr Asp Leu Pro Gly Cys Gly Ser Phe Ser Ser Leu Ser Val Leu Ile
485 490 495

Ile Asp His Asn Ser Val Ser His Pro Ser Ala Asp Phe Phe Gln Ser
500 505 510

58182US002.ST25.txt

Cys Gln Lys Met Arg Ser Ile Lys Ala Gly Asp Asn Pro Phe Gln Cys
515 520 525

Thr Cys Glu Leu Gly Glu Phe Val Lys Asn Ile Asp Gln Val Ser Ser
530 535 540

Glu Val Leu Glu Gly Trp Pro Asp Ser Tyr Lys Cys Asp Tyr Pro Glu
545 550 555 560

Ser Tyr Arg Gly Thr Leu Leu Lys Asp Phe His Met Ser Glu Leu Ser
565 570 575

Cys Asn Ile Thr Leu Leu Ile Val Thr Ile Val Ala Thr Met Leu Val
580 585 590

Leu Ala Val Thr Val Thr Ser Leu Cys Ile Tyr Leu Asp Leu Pro Trp
595 600 605

Tyr Leu Arg Met Val Cys Gln Trp Thr Gln Thr Arg Arg Arg Ala Arg
610 615 620

Asn Ile Pro Leu Glu Glu Leu Gln Arg Asn Leu Gln Phe His Ala Phe
625 630 635 640

Ile Ser Tyr Ser Gly His Asp Ser Phe Trp Val Lys Asn Glu Leu Leu
645 650 655

Pro Asn Leu Glu Lys Glu Gly Met Gln Ile Cys Leu His Glu Arg Asn
660 665 670

Phe Val Pro Gly Lys Ser Ile Val Glu Asn Ile Ile Thr Cys Ile Glu
675 680 685

Lys Ser Tyr Lys Ser Ile Phe Val Leu Ser Pro Asn Phe Val Gln Ser
690 695 700

Glu Trp Cys His Tyr Glu Leu Tyr Phe Ala His His Asn Leu Phe His
705 710 715 720

Glu Gly Ser Asn Ser Leu Ile Leu Ile Leu Leu Glu Pro Ile Pro Gln
725 730 735

Tyr Ser Ile Pro Ser Ser Tyr His Lys Leu Lys Ser Leu Met Ala Arg
740 745 750

Arg Thr Tyr Leu Glu Trp Pro Lys Glu Lys Ser Lys Arg Gly Leu Phe
755 760 765

58182US002.ST25.txt

Trp Ala Asn Leu Arg Ala Ala Ile Asn Ile Lys Leu Thr Glu Gln Ala
 770 775 780

Lys Lys
 785

<210> 3
 <211> 2621
 <212> DNA
 <213> Homo sapiens

<400> 3
 cagtgttttg tggtgcaagc aggatccaaa ggagacctat agtgactccc aggagctctt 60
 agtgaccaag tgaaggtacc tgtggggctc attgtgccca ttgctctttc actgctttca 120
 actggtagtt gtgggttgaa gcaactggaca atgccacata ctttgtggat ggtgtgggtc 180
 ttgggggtca tcatcagcct ctccaaggaa gaatcctcca atcaggcttc tctgtcttgt 240
 gaccgcaatg gtatctgcaa gggcagctca ggatctttta actccattcc ctcagggctc 300
 acagaagctg taaaaagcct tgacctgtcc aacaacagga tcacctacat tagcaacagt 360
 gacctacaga ggtgtgtgaa cctccaggct ctggtgctga catccaatgg aattaacaca 420
 atagaggaag attctttttc ttccctgggc agtcttgaac atttagactt atcctataat 480
 tacttatcta atttatcgtc ttccctgggtc aagccccttt cttctttaac attcttaaac 540
 ttactgggaa atccttacia aaccctaggg gaaacatctc ttttttctca tctcacaaaa 600
 ttgcaaatcc tgagagtggg aaatatggac accttacta agattcaaag aaaagatttt 660
 gctggactta ccttccttga ggaacttgag attgatgctt cagatctaca gagctatgag 720
 ccaaaaagtt tgaagtcaat tcagaatgta agtcatctga tccttcatat gaagcagcat 780
 attttactgc tggagatttt tgtagatggt acaagttccg tggaatgttt ggaactgcga 840
 gatactgatt tggacacttt ccatttttca gaactatcca ctggtgaaac aaattcattg 900
 attaaaaagt ttacatttag aaatgtgaaa atcaccgatg aaagtttggt tcaggttatg 960
 aaacttttga atcagatttc tggattgtta gaattagagt ttgatgactg tacccttaat 1020
 ggagtgggta attttagagc atctgataat gacagagtta tagatccagg taaagtggaa 1080
 acgttaacaa tccggaggct gcatattcca aggttttact tattttatga tctgagcact 1140
 ttatattcac ttacagaaag agttaaaaga atcacagtag aaaacagtaa agtttttctg 1200
 gttccttggt tactttcaca acatttaaaa tcattagaat acttgatct cagtgaaaat 1260
 ttgatggttg aagaatactt gaaaaattca gcctgtgagg atgcctggcc ctctctacia 1320
 actttaattt taaggcaaaa tcatttggca tcattggaaa aaaccggaga gactttgctc 1380
 actctgaaaa acttgactaa cattgatatc agtaagaata gttttcattc tatgcctgaa 1440

58182US002.ST25.txt

acttgtcagt ggccagaaaa gatgaaatat ttgaacttat ccagcacacg aatacacagt 1500
 gtaacaggct gcattcccaa gacactggaa attttagatg ttagcaacaa caatctcaat 1560
 ttattttctt tgaatttgcc gcaactcaaa gaactttata tttccagaaa taagttgatg 1620
 actctaccag atgcctccct cttacccatg ttactagtat tgaaaatcag taggaatgca 1680
 ataactacgt tttctaagga gcaacttgac tcatttcaca cactgaagac tttggaagct 1740
 ggtggcaata acttcatttg ctctgtgaa ttcctctcct tcactcagga gcagcaagca 1800
 ctggccaaag tcttgattga ttggccagca aattacctgt gtgactctcc atcccatgtg 1860
 cgtggccagc aggttcagga tgtccgcctc tcggtgtcgg aatgtcacag gacagcactg 1920
 gtgtctggca tgtgctgtgc tctgttcctg ctgacctgc tcacgggggt cctgtgccac 1980
 cgtttccatg gcctgtggta tatgaaaatg atgtgggcct ggctccaggc caaaaggaag 2040
 cccaggaaag ctcccagcag gaacatctgc tatgatgcat ttgtttctta cagtgagcgg 2100
 gatgcctact ggggtggagaa ccttatggtc caggagctgg agaacttcaa tcccccttc 2160
 aagttgtgtc ttcataagcg ggacttcatt cctggcaagt ggatcattga caatatcatt 2220
 gactccattg aaaagagcca caaaactgtc tttgtgcttt ctgaaaactt tgtgaagagt 2280
 gagtgggtgca agtatgaact ggacttctcc catttccgtc tttttgatga gaacaatgat 2340
 gctgccattc tcattcttct ggagccatt gagaaaaaag ccattcccca gcgcttctgc 2400
 aagctgcgga agataatgaa caccaagacc tacctggagt ggcccatgga cgaggctcag 2460
 cgggaaggat tttgggtaaa tctgagagct gcgataaagt cctagggttcc catatttaag 2520
 accagtcttt gtctagttgg gatctttatg tcactagtta tagttaagtt cattcagaca 2580
 taattatata aaaactacgt ggatgtaccg tcatttgagg a 2621

<210> 4
 <211> 784
 <212> PRT
 <213> Homo sapiens

<400> 4

Met Pro His Thr Leu Trp Met Val Trp Val Leu Gly Val Ile Ile Ser
1 5 10 15

Leu Ser Lys Glu Glu Ser Ser Asn Gln Ala Ser Leu Ser Cys Asp Arg
20 25 30

Asn Gly Ile Cys Lys Gly Ser Ser Gly Ser Leu Asn Ser Ile Pro Ser
35 40 45

Gly Leu Thr Glu Ala Val Lys Ser Leu Asp Leu Ser Asn Asn Arg Ile
50 55 60

58182US002.ST25.txt

Thr Tyr Ile Ser Asn Ser Asp Leu Gln Arg Cys Val Asn Leu Gln Ala
65 70 75 80

Leu Val Leu Thr Ser Asn Gly Ile Asn Thr Ile Glu Glu Asp Ser Phe
85 90 95

Ser Ser Leu Gly Ser Leu Glu His Leu Asp Leu Ser Tyr Asn Tyr Leu
100 105 110

Ser Asn Leu Ser Ser Ser Trp Phe Lys Pro Leu Ser Ser Leu Thr Phe
115 120 125

Leu Asn Leu Leu Gly Asn Pro Tyr Lys Thr Leu Gly Glu Thr Ser Leu
130 135 140

Phe Ser His Leu Thr Lys Leu Gln Ile Leu Arg Val Gly Asn Met Asp
145 150 155 160

Thr Phe Thr Lys Ile Gln Arg Lys Asp Phe Ala Gly Leu Thr Phe Leu
165 170 175

Glu Glu Leu Glu Ile Asp Ala Ser Asp Leu Gln Ser Tyr Glu Pro Lys
180 185 190

Ser Leu Lys Ser Ile Gln Asn Val Ser His Leu Ile Leu His Met Lys
195 200 205

Gln His Ile Leu Leu Leu Glu Ile Phe Val Asp Val Thr Ser Ser Val
210 215 220

Glu Cys Leu Glu Leu Arg Asp Thr Asp Leu Asp Thr Phe His Phe Ser
225 230 235 240

Glu Leu Ser Thr Gly Glu Thr Asn Ser Leu Ile Lys Lys Phe Thr Phe
245 250 255

Arg Asn Val Lys Ile Thr Asp Glu Ser Leu Phe Gln Val Met Lys Leu
260 265 270

Leu Asn Gln Ile Ser Gly Leu Leu Glu Leu Glu Phe Asp Asp Cys Thr
275 280 285

Leu Asn Gly Val Gly Asn Phe Arg Ala Ser Asp Asn Asp Arg Val Ile
290 295 300

Asp Pro Gly Lys Val Glu Thr Leu Thr Ile Arg Arg Leu His Ile Pro
305 310 315 320

58182US002.ST25.txt

Arg Phe Tyr Leu Phe Tyr Asp Leu Ser Thr Leu Tyr Ser Leu Thr Glu
325 330 335

Arg Val Lys Arg Ile Thr Val Glu Asn Ser Lys Val Phe Leu Val Pro
340 345 350

Cys Leu Leu Ser Gln His Leu Lys Ser Leu Glu Tyr Leu Asp Leu Ser
355 360 365

Glu Asn Leu Met Val Glu Glu Tyr Leu Lys Asn Ser Ala Cys Glu Asp
370 375 380

Ala Trp Pro Ser Leu Gln Thr Leu Ile Leu Arg Gln Asn His Leu Ala
385 390 395 400

Ser Leu Glu Lys Thr Gly Glu Thr Leu Leu Thr Leu Lys Asn Leu Thr
405 410 415

Asn Ile Asp Ile Ser Lys Asn Ser Phe His Ser Met Pro Glu Thr Cys
420 425 430

Gln Trp Pro Glu Lys Met Lys Tyr Leu Asn Leu Ser Ser Thr Arg Ile
435 440 445

His Ser Val Thr Gly Cys Ile Pro Lys Thr Leu Glu Ile Leu Asp Val
450 455 460

Ser Asn Asn Asn Leu Asn Leu Phe Ser Leu Asn Leu Pro Gln Leu Lys
465 470 475 480

Glu Leu Tyr Ile Ser Arg Asn Lys Leu Met Thr Leu Pro Asp Ala Ser
485 490 495

Leu Leu Pro Met Leu Leu Val Leu Lys Ile Ser Arg Asn Ala Ile Thr
500 505 510

Thr Phe Ser Lys Glu Gln Leu Asp Ser Phe His Thr Leu Lys Thr Leu
515 520 525

Glu Ala Gly Gly Asn Asn Phe Ile Cys Ser Cys Glu Phe Leu Ser Phe
530 535 540

Thr Gln Glu Gln Gln Ala Leu Ala Lys Val Leu Ile Asp Trp Pro Ala
545 550 555 560

Asn Tyr Leu Cys Asp Ser Pro Ser His Val Arg Gly Gln Gln Val Gln
Page 9

58182US002.ST25.txt
570

565

575

Asp Val Arg Leu Ser Val Ser Glu Cys His Arg Thr Ala Leu Val Ser
 580 585 590
 Gly Met Cys Cys Ala Leu Phe Leu Leu Ile Leu Leu Thr Gly Val Leu
 595 600 605
 Cys His Arg Phe His Gly Leu Trp Tyr Met Lys Met Met Trp Ala Trp
 610 615 620
 Leu Gln Ala Lys Arg Lys Pro Arg Lys Ala Pro Ser Arg Asn Ile Cys
 625 630 635 640
 Tyr Asp Ala Phe Val Ser Tyr Ser Glu Arg Asp Ala Tyr Trp Val Glu
 645 650 655
 Asn Leu Met Val Gln Glu Leu Glu Asn Phe Asn Pro Pro Phe Lys Leu
 660 665 670
 Cys Leu His Lys Arg Asp Phe Ile Pro Gly Lys Trp Ile Ile Asp Asn
 675 680 685
 Ile Ile Asp Ser Ile Glu Lys Ser His Lys Thr Val Phe Val Leu Ser
 690 695 700
 Glu Asn Phe Val Lys Ser Glu Trp Cys Lys Tyr Glu Leu Asp Phe Ser
 705 710 715 720
 His Phe Arg Leu Phe Asp Glu Asn Asn Asp Ala Ala Ile Leu Ile Leu
 725 730 735
 Leu Glu Pro Ile Glu Lys Lys Ala Ile Pro Gln Arg Phe Cys Lys Leu
 740 745 750
 Arg Lys Ile Met Asn Thr Lys Thr Tyr Leu Glu Trp Pro Met Asp Glu
 755 760 765
 Ala Gln Arg Glu Gly Phe Trp Val Asn Leu Arg Ala Ala Ile Lys Ser
 770 775 780

<210> 5
 <211> 3057
 <212> DNA
 <213> Homo sapiens

<400> 5
 cactttcgag agtgccgtct atttgccaca cacttcctg atgaaatgtc tggatttgga 60

58182US002.ST25.txt

ctaaagaaaa aaggaaaggc tagcagtcac ccaacagaat catgagacag actttgcctt	120
gtatctactt ttgggggggc cttttgccct ttgggatgct gtgtgcatcc tccaccacca	180
agtgcactgt tagccatgaa gttgctgact gcagccacct gaagttgact caggtacccg	240
atgatctacc cacaaacata acagtgttga accttaccca taatcaactc agaagattac	300
cagccgcca cttcacaagg tatagccagc taactagctt ggatgtagga tttaacacca	360
tctcaaaact ggagccagaa ttgtgccaga aacttcccat gttaaaagtt ttgaacctcc	420
agcacaatga gctatctcaa ctttctgata aaacctttgc cttctgcacg aatttgactg	480
aactccatct catgtccaac tcaatccaga aaattaaaaa taatcccttt gtcaagcaga	540
agaatttaac cacattagat ctgtctcata atggcttgtc atctacaaaa ttaggaactc	600
aggttcagct ggaaaatctc caagagcttc tattatcaaa caataaaatt caagcgctaa	660
aaagtgaaga actggatatc tttgccatt catcttttaa aaaattagag ttgtcatcga	720
atcaaattaa agagttttct ccagggtgtt ttcacgcaat tggaagatta tttggcctct	780
ttctgaacaa tgtccagctg ggtcccagcc ttacagagaa gctatgtttg gaattagcaa	840
acacaagcat tcggaatctg tctctgagta acagccagct gtccaccacc agcaatacaa	900
ctttcttggg actaaagtgg acaaatctca ctatgctcga tctttcctac aacaacttaa	960
atgtgggttg taacgattcc tttgcttggc ttccacaact agaataattc ttcctagagt	1020
ataataatat acagcatttg ttttctcact ctttgcacgg gcttttcaat gtgaggtacc	1080
tgaatttgaa acggtctttt actaaacaaa gtatttccct tgcctcactc cccaagattg	1140
atgatttttc ttttcagtgg ctaaaatgtt tggagcacct taacatggaa gataatgata	1200
ttccaggcat aaaaagcaat atgttcacag gattgataaa cctgaaatac ttaagtctat	1260
ccaactcctt tacaagtttg cgaactttga caaatgaaac atttgatatca cttgctcatt	1320
ctcccttaca catactcaac ctaaccaaga ataaaatctc aaaaatagag agtgatgctt	1380
tctcttggtt gggccaccta gaagtacttg acctgggcct taatgaaatt gggcaagaac	1440
tcacaggcca ggaatggaga ggtctagaaa atattttcga aatctatctt tcctacaaca	1500
agtacctgca gctgactagg aactcctttg ccttgggtccc aagccttcaa cgactgatgc	1560
tccgaagggt ggcccttaaa aatgtggata gctctccttc accattccag cctcttcgta	1620
acttgaccat tctggatcta agcaacaaca acatagccaa cataaatgat gacatgttgg	1680
agggtcttga gaaactagaa attctcgatt tgcagcataa caacttagca cggctctgga	1740
aacacgcaaa ccctgggtgg cccattttatt tcctaaaggg tctgtctcac ctccacatcc	1800
ttactttgga gtccaacggc tttgacgaga tcccagttga ggtcttcaag gattttattg	1860
aactaaagat catcgattta ggattgaata atttaaacac acttccagca tctgtcttta	1920
ataatcaggt gtctctaaag tcattgaacc ttcagaagaa tctcataaca tccgttgaga	1980

58182US002.ST25.txt

```

agaaggtttt cgggccagct ttcaggaacc tgactgagtt agatatgcgc tttaatccct 2040
ttgattgcac gtgtgaaagt attgcctggt ttgttaattg gattaacgag acccatacca 2100
acatccctga gctgtcaagc cactaccttt gcaacactcc acctcactat catgggttcc 2160
cagtgagact ttttgataca tcatcttgca aagacagtgc cccctttgaa ctctttttca 2220
tgatcaatac cagtatcctg ttgattttta tctttattgt acttctcatc cactttgagg 2280
gctggaggat atctttttat tggaatgttt cagtacatcg agttcttggt ttcaaagaaa 2340
tagacagaca gacagaacag tttgaatatg cagcatatat aattcatgcc tataaagata 2400
aggattgggt ctgggaacat ttctcttcaa tggaaaagga agaccaatct ctcaaatttt 2460
gtctggaaga aagggaacttt gaggcgggtg tttttgaact agaagcaatt gttaacagca 2520
tcaaaagaag cagaaaaatt atttttgtta taacacacca tctattaaaa gaccattat 2580
gcaaaagatt caaggtacat catgcagttc aacaagctat tgaacaaaat ctggattcca 2640
ttatatgggt tttccttgag gagattccag attataaact gaaccatgca ctctgtttgc 2700
gaagaggaat gtttaaactt cactgcatct tgaactggcc agttcagaaa gaacggatag 2760
gtgcctttcg tcataaattg caagtagcac ttggatccaa aaactctgta cattaaattt 2820
atttaaatat tcaattagca aaggagaaac tttctcaatt taaaagttc tatggcaaat 2880
ttaagttttc cataaagggt ttataatttg tttattcata tttgtaaattg attatattct 2940
atcacaatta catctcttct aggaaaatgt gtctccttat ttcaggccta tttttgacaa 3000
ttgacttaat tttaccctaa ataaacata taagcacgta aaaaaaaaaa aaaaaaa 3057

```

<210> 6
 <211> 904
 <212> PRT
 <213> Homo sapiens

<400> 6

Met Arg Gln Thr Leu Pro Cys Ile Tyr Phe Trp Gly Gly Leu Leu Pro
 1 5 10 15

Phe Gly Met Leu Cys Ala Ser Ser Thr Thr Lys Cys Thr Val Ser His
 20 25 30

Glu Val Ala Asp Cys Ser His Leu Lys Leu Thr Gln Val Pro Asp Asp
 35 40 45

Leu Pro Thr Asn Ile Thr Val Leu Asn Leu Thr His Asn Gln Leu Arg
 50 55 60

Arg Leu Pro Ala Ala Asn Phe Thr Arg Tyr Ser Gln Leu Thr Ser Leu
 65 70 75 80

58182US002.ST25.txt

Asp Val Gly Phe Asn Thr Ile Ser Lys Leu Glu Pro Glu Leu Cys Gln
85 90 95

Lys Leu Pro Met Leu Lys Val Leu Asn Leu Gln His Asn Glu Leu Ser
100 105 110

Gln Leu Ser Asp Lys Thr Phe Ala Phe Cys Thr Asn Leu Thr Glu Leu
115 120 125

His Leu Met Ser Asn Ser Ile Gln Lys Ile Lys Asn Asn Pro Phe Val
130 135 140

Lys Gln Lys Asn Leu Ile Thr Leu Asp Leu Ser His Asn Gly Leu Ser
145 150 155 160

Ser Thr Lys Leu Gly Thr Gln Val Gln Leu Glu Asn Leu Gln Glu Leu
165 170 175

Leu Leu Ser Asn Asn Lys Ile Gln Ala Leu Lys Ser Glu Glu Leu Asp
180 185 190

Ile Phe Ala Asn Ser Ser Leu Lys Lys Leu Glu Leu Ser Ser Asn Gln
195 200 205

Ile Lys Glu Phe Ser Pro Gly Cys Phe His Ala Ile Gly Arg Leu Phe
210 215 220

Gly Leu Phe Leu Asn Asn Val Gln Leu Gly Pro Ser Leu Thr Glu Lys
225 230 235 240

Leu Cys Leu Glu Leu Ala Asn Thr Ser Ile Arg Asn Leu Ser Leu Ser
245 250 255

Asn Ser Gln Leu Ser Thr Thr Ser Asn Thr Thr Phe Leu Gly Leu Lys
260 265 270

Trp Thr Asn Leu Thr Met Leu Asp Leu Ser Tyr Asn Asn Leu Asn Val
275 280 285

Val Gly Asn Asp Ser Phe Ala Trp Leu Pro Gln Leu Glu Tyr Phe Phe
290 295 300

Leu Glu Tyr Asn Asn Ile Gln His Leu Phe Ser His Ser Leu His Gly
305 310 315 320

Leu Phe Asn Val Arg Tyr Leu Asn Leu Lys Arg Ser Phe Thr Lys Gln

58182US002.ST25.txt
330

325

335

Ser Ile Ser Leu Ala Ser Leu Pro Lys Ile Asp Asp Phe Ser Phe Gln
340 345 350

Trp Leu Lys Cys Leu Glu His Leu Asn Met Glu Asp Asn Asp Ile Pro
355 360 365

Gly Ile Lys Ser Asn Met Phe Thr Gly Leu Ile Asn Leu Lys Tyr Leu
370 375 380

Ser Leu Ser Asn Ser Phe Thr Ser Leu Arg Thr Leu Thr Asn Glu Thr
385 390 395 400

Phe Val Ser Leu Ala His Ser Pro Leu His Ile Leu Asn Leu Thr Lys
405 410 415

Asn Lys Ile Ser Lys Ile Glu Ser Asp Ala Phe Ser Trp Leu Gly His
420 425 430

Leu Glu Val Leu Asp Leu Gly Leu Asn Glu Ile Gly Gln Glu Leu Thr
435 440 445

Gly Gln Glu Trp Arg Gly Leu Glu Asn Ile Phe Glu Ile Tyr Leu Ser
450 455 460

Tyr Asn Lys Tyr Leu Gln Leu Thr Arg Asn Ser Phe Ala Leu Val Pro
465 470 475 480

Ser Leu Gln Arg Leu Met Leu Arg Arg Val Ala Leu Lys Asn Val Asp
485 490 495

Ser Ser Pro Ser Pro Phe Gln Pro Leu Arg Asn Leu Thr Ile Leu Asp
500 505 510

Leu Ser Asn Asn Asn Ile Ala Asn Ile Asn Asp Asp Met Leu Glu Gly
515 520 525

Leu Glu Lys Leu Glu Ile Leu Asp Leu Gln His Asn Asn Leu Ala Arg
530 535 540

Leu Trp Lys His Ala Asn Pro Gly Gly Pro Ile Tyr Phe Leu Lys Gly
545 550 555 560

Leu Ser His Leu His Ile Leu Asn Leu Glu Ser Asn Gly Phe Asp Glu
565 570 575

58182US002.ST25.txt

Ile Pro Val Glu Val Phe Lys Asp Leu Phe Glu Leu Lys Ile Ile Asp
580 585 590

Leu Gly Leu Asn Asn Leu Asn Thr Leu Pro Ala Ser Val Phe Asn Asn
595 600 605

Gln Val Ser Leu Lys Ser Leu Asn Leu Gln Lys Asn Leu Ile Thr Ser
610 615 620

Val Glu Lys Lys Val Phe Gly Pro Ala Phe Arg Asn Leu Thr Glu Leu
625 630 635 640

Asp Met Arg Phe Asn Pro Phe Asp Cys Thr Cys Glu Ser Ile Ala Trp
645 650 655

Phe Val Asn Trp Ile Asn Glu Thr His Thr Asn Ile Pro Glu Leu Ser
660 665 670

Ser His Tyr Leu Cys Asn Thr Pro Pro His Tyr His Gly Phe Pro Val
675 680 685

Arg Leu Phe Asp Thr Ser Ser Cys Lys Asp Ser Ala Pro Phe Glu Leu
690 695 700

Phe Phe Met Ile Asn Thr Ser Ile Leu Leu Ile Phe Ile Phe Ile Val
705 710 715 720

Leu Leu Ile His Phe Glu Gly Trp Arg Ile Ser Phe Tyr Trp Asn Val
725 730 735

Ser Val His Arg Val Leu Gly Phe Lys Glu Ile Asp Arg Gln Thr Glu
740 745 750

Gln Phe Glu Tyr Ala Ala Tyr Ile Ile His Ala Tyr Lys Asp Lys Asp
755 760 765

Trp Val Trp Glu His Phe Ser Ser Met Glu Lys Glu Asp Gln Ser Leu
770 775 780

Lys Phe Cys Leu Glu Glu Arg Asp Phe Glu Ala Gly Val Phe Glu Leu
785 790 795 800

Glu Ala Ile Val Asn Ser Ile Lys Arg Ser Arg Lys Ile Ile Phe Val
805 810 815

Ile Thr His His Leu Leu Lys Asp Pro Leu Cys Lys Arg Phe Lys Val
820 825 830

58182US002.ST25.txt

His His Ala Val Gln Gln Ala Ile Glu Gln Asn Leu Asp Ser Ile Ile
835 840 845

Leu Val Phe Leu Glu Glu Ile Pro Asp Tyr Lys Leu Asn His Ala Leu
850 855 860

Cys Leu Arg Arg Gly Met Phe Lys Ser His Cys Ile Leu Asn Trp Pro
865 870 875 880

Val Gln Lys Glu Arg Ile Gly Ala Phe Arg His Lys Leu Gln Val Ala
885 890 895

Leu Gly Ser Lys Asn Ser Val His
900

<210> 7
<211> 3811
<212> DNA
<213> Homo sapiens

<400> 7
acagggccac tgctgctcac agaagcagtg aggatgatgc caggatgatg tctgcctcgc 60
gcctggctgg gactctgata ccagccatgg ccttcctctc ctgcgtgaga ccagaaagct 120
gggagccctg cgtggagact tggccctaaa ccacacagaa gagctggcat gaaaccaga 180
gctttcagac tccggagcct cagcccttca ccccgattcc attgcttctt gctaaatgct 240
gccgttttat cacggagggtg gttcctaata ttacttatca atgcatggag ctgaatttct 300
acaaaatccc cgacaacctc cccttctcaa ccaagaacct ggacctgagc tttaatcccc 360
tgaggcattt aggcagctat agcttcttca gtttcccaga actgcagggtg ctggatttat 420
ccagggtgtga aatccagaca attgaagatg gggcatatca gagcctaagc cacctctcta 480
ccttaatat gacaggaaac cccatccaga gtttagccct gggagccttt tctggactat 540
caagtttaca gaagctgggtg gctgtggaga caaatctagc atctctagag aacttcccca 600
ttggacatct caaaactttg aaagaactta atgtggctca caatcttatc caatctttca 660
aattacctga gtatttttct aatctgacca atctagagca cttggacctt tccagcaaca 720
agattcaaag tattttattgc acagacttgc gggttctaca tcaaatgccc ctactcaatc 780
tctctttaga cctgtccctg aaccctatga actttatcca accagggtgca tttaaagaaa 840
ttaggcttca taagctgact ttaagaaata attttgatag tttaaagtga atgaaaactt 900
gtattcaagg tctggctggt ttagaagtcc atcgtttggt tctgggagaa tttagaaatg 960
aaggaaactt ggaaaagttt gacaaatctg ctctagaggg cctgtgcaat ttgaccattg 1020
aagaattccg attagcatac ttagactact acctcgatga tattattgac ttatttaatt 1080

58182US002.ST25.txt

gtttgacaaa	tgtttcttca	ttttccctgg	tgagtgtgac	tattgaaagg	gtaaaagact	1140
tttcttataa	tttcggatgg	caacatttag	aattagttaa	ctgtaaattt	ggacagtttc	1200
ccacattgaa	actcaaactc	ctcaaaaggc	ttactttcac	ttccaacaaa	ggtgggaatg	1260
ctttttcaga	agttgatcta	ccaagccttg	agttttctaga	tctcagtaga	aatggcttga	1320
gtttcaaagg	ttgctgttct	caaagtgatt	ttgggacaac	cagcctaaag	tatttagatc	1380
tgagcttcaa	tggtgttatt	accatgagtt	caaacttctt	gggcttagaa	caactagaac	1440
atctggattt	ccagcattcc	aatttgaaac	aaatgagtga	gttttcagta	ttcctatcac	1500
tcagaaacct	catttacctt	gacatttctc	atactcacac	cagagttgct	ttcaatggca	1560
tcttcaatgg	cttgtccagt	ctcgaagtct	tgaaaatggc	tggcaattct	ttccaggaaa	1620
acttccttcc	agatatcttc	acagagctga	gaaacttgac	cttcctggac	ctctctcagt	1680
gtcaactgga	gcagttgtct	ccaacagcat	ttaactcact	ctccagtctt	caggtactaa	1740
atatgagcca	caacaacttc	ttttcattgg	atacgtttcc	ttataagtgt	ctgaactccc	1800
tccaggttct	tgattacagt	ctcaatcaca	taatgacttc	caaaaaacag	gaactacagc	1860
atthttccaag	tagtctagct	ttcttaaadc	ttactcagaa	tgactttgct	tgtacttgtg	1920
aacaccagag	tttcctgcaa	tggatcaagg	accagaggca	gctcttggtg	gaagttgaac	1980
gaatggaatg	tgcaacacct	tcagataagc	agggcatgcc	tgtgctgagt	ttgaatatca	2040
cctgtcagat	gaataagacc	atcattgggtg	tgctgggtcct	cagtgtgctt	gtagtatctg	2100
ttgtagcagt	tctgggtctat	aagttctatt	ttcacctgat	gcttcttgct	ggctgcataa	2160
agtatggtag	aggtgaaaac	atctatgatg	cctttgttat	ctactcaagc	caggatgagg	2220
actgggtaag	gaatgagcta	gtaaagaatt	tagaagaagg	ggtgcctcca	tttcagctct	2280
gccttcacta	cagagacttt	attcccgggtg	tggccattgc	tgccaacatc	atccatgaag	2340
gtttccataa	aagccgaaag	gtgattgttg	tgggtgtcca	gcacttcatc	cagagccgct	2400
ggtgtatctt	tgaatatgag	attgctcaga	cctggcagtt	tctgagcagt	cgtgctggta	2460
tcactttcat	tgtcctgcag	aaggtggaga	agaccctgct	caggcagcag	gtggagctgt	2520
accgccttct	cagcaggaac	acttacctgg	agtgggagga	cagtgtcctg	gggcggcaca	2580
tcttctggag	acgactcaga	aaagccctgc	tggatggtaa	atcatggaat	ccagaaggaa	2640
cagtgggtac	aggatgcaat	tggcaggaag	caacatctat	ctgaagagga	aaaataaaaa	2700
cctcctgagg	catttcttgc	ccagctgggt	ccaacacttg	ttcagttaat	aagtattaaa	2760
tgctgccaca	tgtcaggcct	tatgctaagg	gtgagtaatt	ccatgggtgca	ctagatatgc	2820
agggtgcta	atctcaagga	gcttccagtg	cagaggggaat	aaatgctaga	ctaaaataca	2880
gagtcttcca	ggtgggcatt	tcaaccaact	cagtcaagga	acccatgaca	aagaaagtca	2940
tttcaactct	tacctcatca	agttgaataa	agacagagaa	aacagaaaga	gacattgttc	3000

58182US002.ST25.txt

```

ttttcctgag tcttttgaat ggaaattgta ttatggtata gccatcataa aaccattttg 3060
gtagttttga ctgaactggg tgttcacttt ttcctttttg attgaataca atttaaattc 3120
tacttgatga ctgcagtcgt caaggggctc ctgatgcaag atgccccttc cattttaagt 3180
ctgtctcctt acagagggtta aagtctaattg gctaattcct aaggaaacct gattaacaca 3240
tgctcacaac catcctgggc attctcgaac atgttctatt tttaactaa tcaccctga 3300
tatattttta tttttatata tccagttttc atttttttac gtcttgcccta taagctaata 3360
tcataaataa ggttgtttaa gacgtgcttc aaatatccat attaaccact atttttcaag 3420
gaagtatgga aaagtacact ctgtcacttt gtcactcgat gtcattccaa agttattgcc 3480
tactaagtaa tgactgtcat gaaagcagca ttgaaataat ttgtttaaag ggggcactct 3540
tttaaacggg aagaaaattt ccgcttcctg gtcttatcat ggacaatttg ggctataggc 3600
atgaaggaag tgggattacc tcaggaagtc accttttctt gattccagaa acatatgggc 3660
tgataaaccc ggggtgacct catgaaatga gttgcagcag atgtttatatt ttttcagaac 3720
aagtgatgtt tgatggacct atgaatctat ttagggagac acagatggct gggatccctc 3780
ccctgtaccc ttctcactga caggagaact a 3811

```

<210> 8
 <211> 799
 <212> PRT
 <213> Homo sapiens

<400> 8

Met Glu Leu Asn Phe Tyr Lys Ile Pro Asp Asn Leu Pro Phe Ser Thr
1 5 10 15

Lys Asn Leu Asp Leu Ser Phe Asn Pro Leu Arg His Leu Gly Ser Tyr
20 25 30

Ser Phe Phe Ser Phe Pro Glu Leu Gln Val Leu Asp Leu Ser Arg Cys
35 40 45

Glu Ile Gln Thr Ile Glu Asp Gly Ala Tyr Gln Ser Leu Ser His Leu
50 55 60

Ser Thr Leu Ile Leu Thr Gly Asn Pro Ile Gln Ser Leu Ala Leu Gly
65 70 75 80

Ala Phe Ser Gly Leu Ser Ser Leu Gln Lys Leu Val Ala Val Glu Thr
85 90 95

Asn Leu Ala Ser Leu Glu Asn Phe Pro Ile Gly His Leu Lys Thr Leu
100 105 110

58182US002.ST25.txt

Lys Glu Leu Asn Val Ala His Asn Leu Ile Gln Ser Phe Lys Leu Pro
115 120 125

Glu Tyr Phe Ser Asn Leu Thr Asn Leu Glu His Leu Asp Leu Ser Ser
130 135 140

Asn Lys Ile Gln Ser Ile Tyr Cys Thr Asp Leu Arg Val Leu His Gln
145 150 155 160

Met Pro Leu Leu Asn Leu Ser Leu Asp Leu Ser Leu Asn Pro Met Asn
165 170 175

Phe Ile Gln Pro Gly Ala Phe Lys Glu Ile Arg Leu His Lys Leu Thr
180 185 190

Leu Arg Asn Asn Phe Asp Ser Leu Asn Val Met Lys Thr Cys Ile Gln
195 200 205

Gly Leu Ala Gly Leu Glu Val His Arg Leu Val Leu Gly Glu Phe Arg
210 215 220

Asn Glu Gly Asn Leu Glu Lys Phe Asp Lys Ser Ala Leu Glu Gly Leu
225 230 235 240

Cys Asn Leu Thr Ile Glu Glu Phe Arg Leu Ala Tyr Leu Asp Tyr Tyr
245 250 255

Leu Asp Asp Ile Ile Asp Leu Phe Asn Cys Leu Thr Asn Val Ser Ser
260 265 270

Phe Ser Leu Val Ser Val Thr Ile Glu Arg Val Lys Asp Phe Ser Tyr
275 280 285

Asn Phe Gly Trp Gln His Leu Glu Leu Val Asn Cys Lys Phe Gly Gln
290 295 300

Phe Pro Thr Leu Lys Leu Lys Ser Leu Lys Arg Leu Thr Phe Thr Ser
305 310 315 320

Asn Lys Gly Gly Asn Ala Phe Ser Glu Val Asp Leu Pro Ser Leu Glu
325 330 335

Phe Leu Asp Leu Ser Arg Asn Gly Leu Ser Phe Lys Gly Cys Cys Ser
340 345 350

Gln Ser Asp Phe Gly Thr Thr Ser Leu Lys Tyr Leu Asp Leu Ser Phe
Page 19

58182US002.ST25.txt
355 360 365

Asn Gly Val Ile Thr Met Ser Ser Asn Phe Leu Gly Leu Glu Gln Leu
370 375 380

Glu His Leu Asp Phe Gln His Ser Asn Leu Lys Gln Met Ser Glu Phe
385 390 395 400

Ser Val Phe Leu Ser Leu Arg Asn Leu Ile Tyr Leu Asp Ile Ser His
405 410 415

Thr His Thr Arg Val Ala Phe Asn Gly Ile Phe Asn Gly Leu Ser Ser
420 425 430

Leu Glu Val Leu Lys Met Ala Gly Asn Ser Phe Gln Glu Asn Phe Leu
435 440 445

Pro Asp Ile Phe Thr Glu Leu Arg Asn Leu Thr Phe Leu Asp Leu Ser
450 455 460

Gln Cys Gln Leu Glu Gln Leu Ser Pro Thr Ala Phe Asn Ser Leu Ser
465 470 475 480

Ser Leu Gln Val Leu Asn Met Ser His Asn Asn Phe Phe Ser Leu Asp
485 490 495

Thr Phe Pro Tyr Lys Cys Leu Asn Ser Leu Gln Val Leu Asp Tyr Ser
500 505 510

Leu Asn His Ile Met Thr Ser Lys Lys Gln Glu Leu Gln His Phe Pro
515 520 525

Ser Ser Leu Ala Phe Leu Asn Leu Thr Gln Asn Asp Phe Ala Cys Thr
530 535 540

Cys Glu His Gln Ser Phe Leu Gln Trp Ile Lys Asp Gln Arg Gln Leu
545 550 555 560

Leu Val Glu Val Glu Arg Met Glu Cys Ala Thr Pro Ser Asp Lys Gln
565 570 575

Gly Met Pro Val Leu Ser Leu Asn Ile Thr Cys Gln Met Asn Lys Thr
580 585 590

Ile Ile Gly Val Ser Val Leu Ser Val Leu Val Val Ser Val Val Ala
595 600 605

58182US002.ST25.txt

Val Leu Val Tyr Lys Phe Tyr Phe His Leu Met Leu Leu Ala Gly Cys
 610 615 620

Ile Lys Tyr Gly Arg Gly Glu Asn Ile Tyr Asp Ala Phe Val Ile Tyr
 625 630 635 640

Ser Ser Gln Asp Glu Asp Trp Val Arg Asn Glu Leu Val Lys Asn Leu
 645 650 655

Glu Glu Gly Val Pro Pro Phe Gln Leu Cys Leu His Tyr Arg Asp Phe
 660 665 670

Ile Pro Gly Val Ala Ile Ala Ala Asn Ile Ile His Glu Gly Phe His
 675 680 685

Lys Ser Arg Lys Val Ile Val Val Val Ser Gln His Phe Ile Gln Ser
 690 695 700

Arg Trp Cys Ile Phe Glu Tyr Glu Ile Ala Gln Thr Trp Gln Phe Leu
 705 710 715 720

Ser Ser Arg Ala Gly Ile Ile Phe Ile Val Leu Gln Lys Val Glu Lys
 725 730 735

Thr Leu Leu Arg Gln Gln Val Glu Leu Tyr Arg Leu Leu Ser Arg Asn
 740 745 750

Thr Tyr Leu Glu Trp Glu Asp Ser Val Leu Gly Arg His Ile Phe Trp
 755 760 765

Arg Arg Leu Arg Lys Ala Leu Leu Asp Gly Lys Ser Trp Asn Pro Glu
 770 775 780

Gly Thr Val Gly Thr Gly Cys Asn Trp Gln Glu Ala Thr Ser Ile
 785 790 795

<210> 9
 <211> 1261
 <212> DNA
 <213> Homo sapiens

<400> 9
 tgttgggatg tttttgaggg actttctcat cttcaagttc tgtatttgaa tcataactat 60
 cttaattccc ttccaccagg agtatttagc catctgactg cattaagggg actaagcctc 120
 aactccaaca ggctgacagt tctttctcac aatgatttac ctgctaattt agagatcctg 180
 gacatatcca ggaaccagct cctagctcct aatcctgatg tatttgtatc acttagtgtc 240
 ttggatataa ctcataacaa gttcatttgt gaatgtgaac ttagcacttt tatcaattgg 300

58182US002.ST25.txt

```

cttaatcaca ccaatgtcac tatagctggg cctcctgcag acatatattg tgtgtaccct 360
gactcgttct ctgggggtttc cctcttctct ctttccacgg aagggttgta tgaagaggaa 420
gtcttaaagt ccctaaagtt ctcccttttc attgtatgca ctgtcactct gactctgttc 480
ctcatgacca tcctcacagt cacaaagttc cggggcttct gttttatctg ttataagaca 540
gcccagagac tgggtgttcaa ggaccatccc cagggcacag aacctgatat gtacaaatat 600
gatgcctatt tgtgcttcag cagcaaagac ttcacatggg tgcagaatgc tttgctcaaa 660
cacctggaca ctcaatacag tgaccaaaac agattcaacc tgtgctttga agaaagagac 720
tttgtcccag gagaaaaccg cattgccaat atccaggatg ccatctggaa cagtagaaag 780
atcgtttgtc ttgtgagcag acacttcctt agagatggct ggtgccttga agccttcagt 840
tatgcccagg gcagggtgctt atctgacctt aacagtgtc tcatcatggg ggtgggttggg 900
tccttgctccc agtaccagtt gatgaaacat caatccatca gaggctttgt acagaaacag 960
cagtatttga ggtggcctga ggatctccag gatgttggct ggtttcttca taaactctct 1020
caacagatac taaagaaaga aaaagaaaag aagaaagaca ataacattcc gttgcaaact 1080
gtagcaacca tctcctaadc aaaggagcaa tttccaactt atctcaagcc acaaataact 1140
cttcactttg tatttgcacc aagttatcat tttgggggtcc tctctggagg tttttttttt 1200
ctttttgcta ctatgaaaac aacataaatc tctcaatttt cgtatcaaaa aaaaaaaaaa 1260
a 1261

```

```

<210> 10
<211> 204
<212> PRT
<213> Homo sapiens

```

```

<400> 10

```

```

Met Thr Ile Leu Thr Val Thr Lys Phe Arg Gly Phe Cys Phe Ile Cys
1           5           10           15

```

```

Tyr Lys Thr Ala Gln Arg Leu Val Phe Lys Asp His Pro Gln Gly Thr
20           25           30

```

```

Glu Pro Asp Met Tyr Lys Tyr Asp Ala Tyr Leu Cys Phe Ser Ser Lys
35           40           45

```

```

Asp Phe Thr Trp Val Gln Asn Ala Leu Leu Lys His Leu Asp Thr Gln
50           55           60

```

```

Tyr Ser Asp Gln Asn Arg Phe Asn Leu Cys Phe Glu Glu Arg Asp Phe
65           70           75           80

```

58182US002.ST25.txt

Val Pro Gly Glu Asn Arg Ile Ala Asn Ile Gln Asp Ala Ile Trp Asn
 85 90 95

Ser Arg Lys Ile Val Cys Leu Val Ser Arg His Phe Leu Arg Asp Gly
 100 105 110

Trp Cys Leu Glu Ala Phe Ser Tyr Ala Gln Gly Arg Cys Leu Ser Asp
 115 120 125

Leu Asn Ser Ala Leu Ile Met Val Val Val Gly Ser Leu Ser Gln Tyr
 130 135 140

Gln Leu Met Lys His Gln Ser Ile Arg Gly Phe Val Gln Lys Gln Gln
 145 150 155 160

Tyr Leu Arg Trp Pro Glu Asp Leu Gln Asp Val Gly Trp Phe Leu His
 165 170 175

Lys Leu Ser Gln Gln Ile Leu Lys Lys Glu Lys Glu Lys Lys Lys Asp
 180 185 190

Asn Asn Ile Pro Leu Gln Thr Val Ala Thr Ile Ser
 195 200

<210> 11
 <211> 2753
 <212> DNA
 <213> Homo sapiens

<400> 11
 agaatttgga ctcatatcaa gatgctctga agaagaacaa cccttttagga tagccactgc 60
 aacatcatga ccaaagacaa agaacctatt gttaaaagct tccattttgt ttgccttatg 120
 atcataatag ttggaaccag aatccagttc tccgacggaa atgaatttgc agtagacaag 180
 tcaaaaagag gtcttattca tgttccaaaa gacctaccgc tgaaaaccaa agtcttagat 240
 atgtctcaga actacatcgc tgagcttcag gtctctgaca tgagctttct atcagagttg 300
 acagttttga gactttccca taacagaatc cagctacttg atttaagtgt tttcaagttc 360
 aaccaggatt tagaatatct ggatttatct cataatcagt tgcaaaagat atcctgccat 420
 cctattgtga gtttcaggca tttagatctc tcattcaatg atttcaaggc cctgccccatc 480
 tgtaaggaat ttggcaactt atcacaactg aatttcttgg gattgagtg tatgaagctg 540
 caaaaattag atttgctgcc aattgctcac ttgcatctaa gttatatcct tctggattta 600
 agaaattatt atataaaaga aaatgagaca gaaagtctac aaattctgaa tgcaaaaacc 660
 cttcaccttg tttttcaccc aactagttta ttcgctatcc aagtgaacat atcagttaat 720
 actttagggt gcttacaact gactaatatt aaattgaatg atgacaactg tcaagttttc 780

58182US002.ST25.txt

attaaatttt	tatcagaact	caccagaggt	tcaaccttac	tgaattttac	cctcaaccac	840
atagaaacga	cttggaatg	cctgggcaga	gtctttcaat	ttctttggcc	caaacctgtg	900
gaatatctca	atatttaca	tttaacaata	attgaaagca	ttcgtgaaga	agattttact	960
tattctaaaa	cgacattgaa	agcattgaca	atagaacata	tcacgaacca	agtttttctg	1020
ttttcacaga	cagctttgta	caccgtgttt	tctgagatga	acattatgat	gttaaccatt	1080
tcagatacac	cttttataca	catgctgtgt	cctcatgcac	caagcacatt	caagtttttg	1140
aactttaccc	agaacgtttt	cacagatagt	atttttgaaa	aatgttccac	gttagttaaa	1200
ttggagacac	ttatcttaca	aaaaaatgga	ttaaaagacc	ttttcaaagt	aggtctcatg	1260
acgaaggata	tgccttcttt	ggaaatactg	gatgttagct	ggaattcttt	ggaatctggt	1320
agacataaag	aaaactgcac	ttgggttgag	agtatagtgg	tgttaaattt	gtcttcaaat	1380
atgcttactg	actctgtttt	cagatgttta	cctcccagga	tcaaggtact	tgatcttcac	1440
agcaataaaa	taaagagcgt	tcctaaacaa	gtcgtaaaac	tggaagcttt	gcaagaactc	1500
aatgttgctt	tcaattcttt	aactgacctt	cctggatgtg	gcagcttttag	cagcctttct	1560
gtattgatca	ttgatcaca	ttcagtttcc	cacccatcgg	ctgatttctt	ccagagctgc	1620
cagaagatga	ggtcaataaa	agcaggggac	aatccattcc	aatgtacctg	tgagctaaga	1680
gaatttgatca	aaaatataga	ccaagtatca	agtgaagtgt	tagagggtg	gcctgattct	1740
tataagtgtg	actaccaga	aagttataga	ggaagcccac	taaaggactt	tcacatgtct	1800
gaattatcct	gcaacataac	tctgctgac	gtcaccatcg	gtgccaccat	gctggtgttg	1860
gctgtgactg	tgacctccct	ctgcatctac	ttggatctgc	cctggtatct	caggatggtg	1920
tgccagtgga	cccagactcg	gcgcagggcc	aggaacatac	ccttagaaga	actccaaaga	1980
aacctccagt	ttcatgcttt	tatttcatat	agtgaacatg	attctgcctg	ggtgaaaagt	2040
gaattggtac	cttacctaga	aaaagaagat	atacagattt	gtcttcatga	gaggaacttt	2100
gtccctggca	agagcattgt	ggaaaatatc	atcaactgca	ttgagaagag	ttacaagtcc	2160
atctttgttt	tgtctcccaa	ctttgtccag	agtgagtgg	gccattacga	actctatttt	2220
gcccatacaca	atctctttca	tgaaggatct	aataacttaa	tcctcatctt	actggaaccc	2280
attccacaga	acagcattcc	caacaagtac	cacaagctga	aggctctcat	gacgcagcgg	2340
acttatttgc	agtggcccaa	ggagaaaagc	aaacgtgggc	tcttttgggc	taacattaga	2400
gccgctttta	atatgaaatt	aacactagtc	actgaaaaca	atgatgtgaa	atcttaaaaa	2460
aatttaggaa	attcaactta	agaaaccatt	atttacttgg	atgatggtga	atagtacagt	2520
cgtaagtaac	tgtctggagg	tgctccatt	atcctcatgc	cttcaggaaa	gacttaacaa	2580
aaacaatggt	tcctctgggg	aactgagcta	ggcggtgagg	ttagcctgcc	agttagagac	2640

58182US002.ST25.txt

agcccagtcct cttctgggttt aatcattatg tttcaaattg aaacagtcctc ttttgagtaa 2700

atgctcagtt tttcagctcc tctccactct gctttcccaa atggattctg ttg 2753

<210> 12

<211> 796

<212> PRT

<213> Homo sapiens

<400> 12

Met Thr Lys Asp Lys Glu Pro Ile Val Lys Ser Phe His Phe Val Cys
1 5 10 15Leu Met Ile Ile Ile Val Gly Thr Arg Ile Gln Phe Ser Asp Gly Asn
20 25 30Glu Phe Ala Val Asp Lys Ser Lys Arg Gly Leu Ile His Val Pro Lys
35 40 45Asp Leu Pro Leu Lys Thr Lys Val Leu Asp Met Ser Gln Asn Tyr Ile
50 55 60Ala Glu Leu Gln Val Ser Asp Met Ser Phe Leu Ser Glu Leu Thr Val
65 70 75 80Leu Arg Leu Ser His Asn Arg Ile Gln Leu Leu Asp Leu Ser Val Phe
85 90 95Lys Phe Asn Gln Asp Leu Glu Tyr Leu Asp Leu Ser His Asn Gln Leu
100 105 110Gln Lys Ile Ser Cys His Pro Ile Val Ser Phe Arg His Leu Asp Leu
115 120 125Ser Phe Asn Asp Phe Lys Ala Leu Pro Ile Cys Lys Glu Phe Gly Asn
130 135 140Leu Ser Gln Leu Asn Phe Leu Gly Leu Ser Ala Met Lys Leu Gln Lys
145 150 155 160Leu Asp Leu Leu Pro Ile Ala His Leu His Leu Ser Tyr Ile Leu Leu
165 170 175Asp Leu Arg Asn Tyr Tyr Ile Lys Glu Asn Glu Thr Glu Ser Leu Gln
180 185 190Ile Leu Asn Ala Lys Thr Leu His Leu Val Phe His Pro Thr Ser Leu
195 200 205

58182US002.ST25.txt

Phe Ala Ile Gln Val Asn Ile Ser Val Asn Thr Leu Gly Cys Leu Gln
 210 215 220
 Leu Thr Asn Ile Lys Leu Asn Asp Asp Asn Cys Gln Val Phe Ile Lys
 225 230 235 240
 Phe Leu Ser Glu Leu Thr Arg Gly Ser Thr Leu Leu Asn Phe Thr Leu
 245 250 255
 Asn His Ile Glu Thr Thr Trp Lys Cys Leu Val Arg Val Phe Gln Phe
 260 265 270
 Leu Trp Pro Lys Pro Val Glu Tyr Leu Asn Ile Tyr Asn Leu Thr Ile
 275 280 285
 Ile Glu Ser Ile Arg Glu Glu Asp Phe Thr Tyr Ser Lys Thr Thr Leu
 290 295 300
 Lys Ala Leu Thr Ile Glu His Ile Thr Asn Gln Val Phe Leu Phe Ser
 305 310 315 320
 Gln Thr Ala Leu Tyr Thr Val Phe Ser Glu Met Asn Ile Met Met Leu
 325 330 335
 Thr Ile Ser Asp Thr Pro Phe Ile His Met Leu Cys Pro His Ala Pro
 340 345 350
 Ser Thr Phe Lys Phe Leu Asn Phe Thr Gln Asn Val Phe Thr Asp Ser
 355 360 365
 Ile Phe Glu Lys Cys Ser Thr Leu Val Lys Leu Glu Thr Leu Ile Leu
 370 375 380
 Gln Lys Asn Gly Leu Lys Asp Leu Phe Lys Val Gly Leu Met Thr Lys
 385 390 395 400
 Asp Met Pro Ser Leu Glu Ile Leu Asp Val Ser Trp Asn Ser Leu Glu
 405 410 415
 Ser Gly Arg His Lys Glu Asn Cys Thr Trp Val Glu Ser Ile Val Val
 420 425 430
 Leu Asn Leu Ser Ser Asn Met Leu Thr Asp Ser Val Phe Arg Cys Leu
 435 440 445
 Pro Pro Arg Ile Lys Val Leu Asp Leu His Ser Asn Lys Ile Lys Ser
 450 455 460

58182US002.ST25.txt

Val Pro Lys Gln Val Val Lys Leu Glu Ala Leu Gln Glu Leu Asn Val
465 470 475 480

Ala Phe Asn Ser Leu Thr Asp Leu Pro Gly Cys Gly Ser Phe Ser Ser
485 490 495

Leu Ser Val Leu Ile Ile Asp His Asn Ser Val Ser His Pro Ser Ala
500 505 510

Asp Phe Phe Gln Ser Cys Gln Lys Met Arg Ser Ile Lys Ala Gly Asp
515 520 525

Asn Pro Phe Gln Cys Thr Cys Glu Leu Arg Glu Phe Val Lys Asn Ile
530 535 540

Asp Gln Val Ser Ser Glu Val Leu Glu Gly Trp Pro Asp Ser Tyr Lys
545 550 555 560

Cys Asp Tyr Pro Glu Ser Tyr Arg Gly Ser Pro Leu Lys Asp Phe His
565 570 575

Met Ser Glu Leu Ser Cys Asn Ile Thr Leu Leu Ile Val Thr Ile Gly
580 585 590

Ala Thr Met Leu Val Leu Ala Val Thr Val Thr Ser Leu Cys Ile Tyr
595 600 605

Leu Asp Leu Pro Trp Tyr Leu Arg Met Val Cys Gln Trp Thr Gln Thr
610 615 620

Arg Arg Arg Ala Arg Asn Ile Pro Leu Glu Glu Leu Gln Arg Asn Leu
625 630 635 640

Gln Phe His Ala Phe Ile Ser Tyr Ser Glu His Asp Ser Ala Trp Val
645 650 655

Lys Ser Glu Leu Val Pro Tyr Leu Glu Lys Glu Asp Ile Gln Ile Cys
660 665 670

Leu His Glu Arg Asn Phe Val Pro Gly Lys Ser Ile Val Glu Asn Ile
675 680 685

Ile Asn Cys Ile Glu Lys Ser Tyr Lys Ser Ile Phe Val Leu Ser Pro
690 695 700

Asn Phe Val Gln Ser Glu Trp Cys His Tyr Glu Leu Tyr Phe Ala His
Page 27

58182US002.ST25.txt
715

705

710

720

His Asn Leu Phe His Glu Gly Ser Asn Asn Leu Ile Leu Ile Leu Leu
725 730 735

Glu Pro Ile Pro Gln Asn Ser Ile Pro Asn Lys Tyr His Lys Leu Lys
740 745 750

Ala Leu Met Thr Gln Arg Thr Tyr Leu Gln Trp Pro Lys Glu Lys Ser
755 760 765

Lys Arg Gly Leu Phe Trp Ala Asn Ile Arg Ala Ala Phe Asn Met Lys
770 775 780

Leu Thr Leu Val Thr Glu Asn Asn Asp Val Lys Ser
785 790 795

<210> 13
<211> 5007
<212> DNA
<213> Homo sapiens

<400> 13
actccagata taggatcact ccatgccatc aagaaagttg atgctattgg gcccatctca 60
agctgatctt ggcacctctc atgctctgct ctcttcaacc agacctctac attccatttt 120
ggaagaagac taaaaatggt gtttccaatg tggacactga agagacaaat tcttatcctt 180
tttaacataa tcctaatttc caaactcctt ggggctagat ggtttcctaa aactctgccc 240
tgtgatgtca ctctggatgt tccaaagaac catgtgatcg tggactgcac agacaagcat 300
ttgacagaaa ttcttgaggg tattcccacg aacaccacga acctcaccct caccattaac 360
cacataccag acatctcccc agcgtccttt cacagactgg accatctggt agagatcgat 420
ttcagatgca actgtgtacc tattccactg ggggtcaaaaa acaacatgtg catcaagagg 480
ctgcagatta aaccagaag ctttagtgga ctcaacttatt taaaatccct ttacctggat 540
ggaaaccagc tactagagat accgcagggc ctcccgcta gcttacagct tctcagcctt 600
gaggccaaca acatcttttc catcagaaaa gagaatctaa cagaactggc caacatagaa 660
atactctacc tgggcaaaaa ctgttattat cgaaatcctt gttatgtttc atattcaata 720
gagaaagatg ctttcctaaa cttgacaaag ttaaaagtgc tctccctgaa agataacaat 780
gtcacagccg tccctactgt tttgcatct actttaacag aactatatct ctacaacaac 840
atgattgcaa aaatccaaga agatgatttt aataacctca accaattaca aattcttgac 900
ctaagtggaa attgccctcg ttgttataat gcccatttc cttgtgcgcc gtgtaaaaat 960
aattctcccc tacagatccc tgtaaagtct tttgatgcgc tgacagaatt aaaagtttta 1020

58182US002.ST25.txt

cgtctacaca gtaactctct tcagcatgtg cccccaagat ggtttaagaa catcaacaaa	1080
ctccaggaac tggatctgtc ccaaaacttc ttggccaaag aaattgggga tgctaaattt	1140
ctgcattttc tccccagcct catccaattg gatctgtctt tcaattttga acttcagggtc	1200
tatcgtgcat ctatgaatct atcacaagca ttttcttcac tgaaaagcct gaaaattctg	1260
cggatcagag gatatgtctt taaagagttg aaaagcttta acctctcgcc attacataat	1320
cttcaaaatc ttgaagttct tgatcttggc actaacttta taaaaattgc taacctcagc	1380
atgttttaac aattttaaag actgaaagtc atagatcttt cagtgaataa aatatcacct	1440
tcaggagatt caagtgaagt tggcttctgc tcaaatgcca gaacttctgt agaaagttat	1500
gaaccccagg tcctggaaca attacattat ttcagatatg ataagtatgc aaggagttgc	1560
agattcaaaa acaaagaggc ttctttcatg tctgttaatg aaagctgcta caagtatggg	1620
cagaccttgg atctaagtaa aaatagtata tttttgtca agtcctctga ttttcagcat	1680
ctttctttcc tcaaatgcct gaatctgtca ggaaatctca ttagccaaac tcttaatggc	1740
agtgaattcc aacctttagc agagctgaga tatttggact tctccaacaa ccggcttgat	1800
ttactccatt caacagcatt tgaagagctt cacaaactgg aagttctgga tataagcagt	1860
aatagccatt attttcaatc agaaggaatt actcatatgc taaactttac caagaaccta	1920
aaggttctgc agaaactgat gatgaacgac aatgacatct cttcctccac cagcaggacc	1980
atggagagtg agtctcttag aactctggaa ttcagaggaa atcacttaga tgttttatgg	2040
agagaagggtg ataacagata cttacaatta ttcaagaatc tgctaaaatt agaggaatta	2100
gacatctcta aaaattccct aagtttcttg ctttctggag tttttgatgg tatgcctcca	2160
aatctaaaga atctctcttt ggccaaaaat gggctcaaat ctttcagttg gaagaaactc	2220
cagtgtctaa agaacctgga aactttggac ctcagccaca accaactgac cactgtccct	2280
gagagattat ccaactgttc cagaagcctc aagaatctga ttcttaagaa taatcaaatc	2340
aggagtctga cgaagtattt tctacaagat gccttccagt tgcgatatct ggatctcagc	2400
tcaaataaaa tccagatgat ccaaaagacc agcttcccag aaaatgtcct caacaatctg	2460
aagatgttgc ttttgcata taatcggttt ctgtgcacct gtgatgctgt gtggtttgtc	2520
tggtgggtta accatacgga ggtgactatt ccttacctgg ccacagatgt gacttgtgtg	2580
gggccaggag cacacaaggg ccaaagtgtg atctccctgg atctgtacac ctgtgagtta	2640
gatctgacta acctgattct gttctcactt tccatatctg tatctctctt tctcatgggtg	2700
atgatgacag caagtcacct ctatttctgg gatgtgtggt atatttacca tttctgtaag	2760
gccaagataa aggggtatca gcgtctaata tcaccagact gttgctatga tgcttttatt	2820
gtgtatgaca ctaaagaccc agctgtgacc gagtgggttt tggctgagct ggtggccaaa	2880
ctggaagacc caagagagaa acattttaat ttatgtctcg aggaaaggga ctggttacca	2940

58182US002.ST25.txt

gggcagccag ttctggaaaa cttttcccag agcatacagc ttagcaaaaa gacagtgttt 3000
gtgatgacag acaagtatgc aaagactgaa aattttaaga tagcatttta cttgtcccat 3060
cagaggctca tggatgaaaa agttgatgtg attatcttga tatttcttga gaagcccttt 3120
cagaagtcca agttcctcca gctccggaaa aggctctgtg ggagttctgt ccttgagtgg 3180
ccaacaaacc cgcaagctca ccatacttc tggcagtgtc taaagaacgc cctggccaca 3240
gacaatcatg tggcctatag tcagggtgttc aaggaaacgg tctagccctt ctttgcaaaa 3300
cacaactgcc tagtttacca aggagaggcc tggctgttta aattgttttc atatatatca 3360
caccaaaagc gtgttttgaa attcttcaag aaatgagatt gcccatattt caggggagcc 3420
accaacgtct gtcacaggag ttggaaagat ggggtttata taatgcatca agtcttcttt 3480
cttatctctc tgtgtctcta tttgcacttg agtctctcac ctgagctcct gtaaaagagt 3540
ggcaagtaaa aaacatgggg ctctgattct cctgtaattg tgataattaa atatacacac 3600
aatcatgaca ttgagaagaa ctgcatttct acccttaaaa agtactggta tatacagaaa 3660
taggggttaa aaaaactcaa gctctctcta tatgagacca aaatgtacta gagttagttt 3720
agtgaataaa aaaaccagtc agctggccgg gcatgggtggc tcatgcttgt aatcccagca 3780
ctttgggagg ccgaggcagg tggatcacga ggtcaggagt ttgagaccag tctggccaac 3840
atggtgaaac cccgtctgta ctaaaaatac aaaaattagc tgggcgtggg ggtgggtgcc 3900
tgtaatccca gctacttggg aggtgaggc aggagaatcg cttgaacccg ggaggtggag 3960
gtggcagtga gccgagatca cgccactgca atgcagcccg ggcaacagag ctagactgtc 4020
tcaaaagaac aaaaaaaaaa aaacacaaaa aaactcagtc agcttcttaa ccaattgctt 4080
ccgtgtcatc cagggcccca ttctgtgcag attgagtgtg ggcaccacac aggtggttgc 4140
tgcttcagtg cttcctgctc tttttccttg ggcctgcttc tgggttccat agggaaacag 4200
taagaaagaa agacacatcc ttaccataaa tgcatatggg ccacctacaa atagaaaaat 4260
atttaaataa tctgccttta tacaaagtga tattctctac ctttgataat ttacctgctt 4320
aaatgttttt atctgcactg caaagtactg tatccaaagt aaaatttcct catccaatat 4380
ctttcaaact gttttgttaa ctaatgccat atatttgtaa gtatctgcac acttgataca 4440
gcaacgtag atggttttga tggtaaacc taaaggagga ctccaagagt gtgtatttat 4500
ttatagtttt atcagagatg acaattattt gaatgccaat tatatggatt cttttcattt 4560
tttgctggag gatgggagaa gaaaccaaag tttatagacc ttcacattga gaaagcttca 4620
gttttgaact tcagctatca gattcaaaaa caacagaaag aaccaagaca ttcttaagat 4680
gcctgtactt tcagctgggt ataaattcat gagttcaaag attgaaacct gaccaatttg 4740
ctttatttca tggaagaagt gatctacaaa ggtgtttgtg ccatttgga aacagcgtgc 4800

58182US002.ST25.txt

```

atgtgttcaa gccttagatt ggcgatgtcg tattttcctc acgtgtggca atgccaaagg 4860
ctttacttta cctgtgagta cacactatat gaattatttc caacgtacat ttaatcaata 4920
agggtcacia attcccaaatt caatctctgg aataaataga gaggtaatta aattgctgga 4980
gccaaactatt tcacaacttc tgtaagc 5007

```

<210> 14
 <211> 1049
 <212> PRT
 <213> Homo sapiens

<400> 14

Met Val Phe Pro Met Trp Thr Leu Lys Arg Gln Ile Leu Ile Leu Phe
 1 5 10 15

Asn Ile Ile Leu Ile Ser Lys Leu Leu Gly Ala Arg Trp Phe Pro Lys
 20 25 30

Thr Leu Pro Cys Asp Val Thr Leu Asp Val Pro Lys Asn His Val Ile
 35 40 45

Val Asp Cys Thr Asp Lys His Leu Thr Glu Ile Pro Gly Gly Ile Pro
 50 55 60

Thr Asn Thr Thr Asn Leu Thr Leu Thr Ile Asn His Ile Pro Asp Ile
 65 70 75 80

Ser Pro Ala Ser Phe His Arg Leu Asp His Leu Val Glu Ile Asp Phe
 85 90 95

Arg Cys Asn Cys Val Pro Ile Pro Leu Gly Ser Lys Asn Asn Met Cys
 100 105 110

Ile Lys Arg Leu Gln Ile Lys Pro Arg Ser Phe Ser Gly Leu Thr Tyr
 115 120 125

Leu Lys Ser Leu Tyr Leu Asp Gly Asn Gln Leu Leu Glu Ile Pro Gln
 130 135 140

Gly Leu Pro Pro Ser Leu Gln Leu Leu Ser Leu Glu Ala Asn Asn Ile
 145 150 155 160

Phe Ser Ile Arg Lys Glu Asn Leu Thr Glu Leu Ala Asn Ile Glu Ile
 165 170 175

Leu Tyr Leu Gly Gln Asn Cys Tyr Tyr Arg Asn Pro Cys Tyr Val Ser
 180 185 190

58182US002.ST25.txt

Tyr Ser Ile Glu Lys Asp Ala Phe Leu Asn Leu Thr Lys Leu Lys Val
195 200 205

Leu Ser Leu Lys Asp Asn Asn Val Thr Ala Val Pro Thr Val Leu Pro
210 215 220

Ser Thr Leu Thr Glu Leu Tyr Leu Tyr Asn Asn Met Ile Ala Lys Ile
225 230 235 240

Gln Glu Asp Asp Phe Asn Asn Leu Asn Gln Leu Gln Ile Leu Asp Leu
245 250 255

Ser Gly Asn Cys Pro Arg Cys Tyr Asn Ala Pro Phe Pro Cys Ala Pro
260 265 270

Cys Lys Asn Asn Ser Pro Leu Gln Ile Pro Val Asn Ala Phe Asp Ala
275 280 285

Leu Thr Glu Leu Lys Val Leu Arg Leu His Ser Asn Ser Leu Gln His
290 295 300

Val Pro Pro Arg Trp Phe Lys Asn Ile Asn Lys Leu Gln Glu Leu Asp
305 310 315 320

Leu Ser Gln Asn Phe Leu Ala Lys Glu Ile Gly Asp Ala Lys Phe Leu
325 330 335

His Phe Leu Pro Ser Leu Ile Gln Leu Asp Leu Ser Phe Asn Phe Glu
340 345 350

Leu Gln Val Tyr Arg Ala Ser Met Asn Leu Ser Gln Ala Phe Ser Ser
355 360 365

Leu Lys Ser Leu Lys Ile Leu Arg Ile Arg Gly Tyr Val Phe Lys Glu
370 375 380

Leu Lys Ser Phe Asn Leu Ser Pro Leu His Asn Leu Gln Asn Leu Glu
385 390 395 400

Val Leu Asp Leu Gly Thr Asn Phe Ile Lys Ile Ala Asn Leu Ser Met
405 410 415

Phe Lys Gln Phe Lys Arg Leu Lys Val Ile Asp Leu Ser Val Asn Lys
420 425 430

Ile Ser Pro Ser Gly Asp Ser Ser Glu Val Gly Phe Cys Ser Asn Ala
435 440 445

58182US002.ST25.txt

Arg Thr Ser Val Glu Ser Tyr Glu Pro Gln Val Leu Glu Gln Leu His
450 455 460

Tyr Phe Arg Tyr Asp Lys Tyr Ala Arg Ser Cys Arg Phe Lys Asn Lys
465 470 475 480

Glu Ala Ser Phe Met Ser Val Asn Glu Ser Cys Tyr Lys Tyr Gly Gln
485 490 495

Thr Leu Asp Leu Ser Lys Asn Ser Ile Phe Phe Val Lys Ser Ser Asp
500 505 510

Phe Gln His Leu Ser Phe Leu Lys Cys Leu Asn Leu Ser Gly Asn Leu
515 520 525

Ile Ser Gln Thr Leu Asn Gly Ser Glu Phe Gln Pro Leu Ala Glu Leu
530 535 540

Arg Tyr Leu Asp Phe Ser Asn Asn Arg Leu Asp Leu Leu His Ser Thr
545 550 555 560

Ala Phe Glu Glu Leu His Lys Leu Glu Val Leu Asp Ile Ser Ser Asn
565 570 575

Ser His Tyr Phe Gln Ser Glu Gly Ile Thr His Met Leu Asn Phe Thr
580 585 590

Lys Asn Leu Lys Val Leu Gln Lys Leu Met Met Asn Asp Asn Asp Ile
595 600 605

Ser Ser Ser Thr Ser Arg Thr Met Glu Ser Glu Ser Leu Arg Thr Leu
610 615 620

Glu Phe Arg Gly Asn His Leu Asp Val Leu Trp Arg Glu Gly Asp Asn
625 630 635 640

Arg Tyr Leu Gln Leu Phe Lys Asn Leu Leu Lys Leu Glu Glu Leu Asp
645 650 655

Ile Ser Lys Asn Ser Leu Ser Phe Leu Pro Ser Gly Val Phe Asp Gly
660 665 670

Met Pro Pro Asn Leu Lys Asn Leu Ser Leu Ala Lys Asn Gly Leu Lys
675 680 685

Ser Phe Ser Trp Lys Lys Leu Gln Cys Leu Lys Asn Leu Glu Thr Leu
Page 33

58182US002.ST25.txt
700

690

695

Asp Leu Ser His Asn Gln Leu Thr Thr Val Pro Glu Arg Leu Ser Asn
705 710 715 720

Cys Ser Arg Ser Leu Lys Asn Leu Ile Leu Lys Asn Asn Gln Ile Arg
725 730 735

Ser Leu Thr Lys Tyr Phe Leu Gln Asp Ala Phe Gln Leu Arg Tyr Leu
740 745 750

Asp Leu Ser Ser Asn Lys Ile Gln Met Ile Gln Lys Thr Ser Phe Pro
755 760 765

Glu Asn Val Leu Asn Asn Leu Lys Met Leu Leu Leu His His Asn Arg
770 775 780

Phe Leu Cys Thr Cys Asp Ala Val Trp Phe Val Trp Trp Val Asn His
785 790 795 800

Thr Glu Val Thr Ile Pro Tyr Leu Ala Thr Asp Val Thr Cys Val Gly
805 810 815

Pro Gly Ala His Lys Gly Gln Ser Val Ile Ser Leu Asp Leu Tyr Thr
820 825 830

Cys Glu Leu Asp Leu Thr Asn Leu Ile Leu Phe Ser Leu Ser Ile Ser
835 840 845

Val Ser Leu Phe Leu Met Val Met Met Thr Ala Ser His Leu Tyr Phe
850 855 860

Trp Asp Val Trp Tyr Ile Tyr His Phe Cys Lys Ala Lys Ile Lys Gly
865 870 875 880

Tyr Gln Arg Leu Ile Ser Pro Asp Cys Cys Tyr Asp Ala Phe Ile Val
885 890 895

Tyr Asp Thr Lys Asp Pro Ala Val Thr Glu Trp Val Leu Ala Glu Leu
900 905 910

Val Ala Lys Leu Glu Asp Pro Arg Glu Lys His Phe Asn Leu Cys Leu
915 920 925

Glu Glu Arg Asp Trp Leu Pro Gly Gln Pro Val Leu Glu Asn Leu Ser
930 935 940

58182US002.ST25.txt

Gln Ser Ile Gln Leu Ser Lys Lys Thr Val Phe Val Met Thr Asp Lys
 945 950 955 960

Tyr Ala Lys Thr Glu Asn Phe Lys Ile Ala Phe Tyr Leu Ser His Gln
 965 970 975

Arg Leu Met Asp Glu Lys Val Asp Val Ile Ile Leu Ile Phe Leu Glu
 980 985 990

Lys Pro Phe Gln Lys Ser Lys Phe Leu Gln Leu Arg Lys Arg Leu Cys
 995 1000 1005

Gly Ser Ser Val Leu Glu Trp Pro Thr Asn Pro Gln Ala His Pro
 1010 1015 1020

Tyr Phe Trp Gln Cys Leu Lys Asn Ala Leu Ala Thr Asp Asn His
 1025 1030 1035

Val Ala Tyr Ser Gln Val Phe Lys Glu Thr Val
 1040 1045

<210> 15
 <211> 3311
 <212> DNA
 <213> Homo sapiens

<400> 15
 ttctgcgctg ctgcaagtta cggaatgaaa aattagaaca acagaaacat ggaaaacatg 60
 ttccttcagt cgtcaatgct gacctgcatt ttcctgctaa tatctggttc ctgtgagtta 120
 tgcgccgaag aaaatttttc tagaagctat ccttgtgatg agaaaaagca aaatgactca 180
 gttattgcag agtgcagcaa tcgtcgacta caggaagttc cccaaacggt gggcaaata 240
 gtgacagaac tagacctgtc tgataatttc atcacacaca taacgaatga atcatttcaa 300
 gggctgcaaa atctcactaa aataaatcta aaccacaacc ccaatgtaca gcaccagaac 360
 ggaaatcccg gtatacaatc aaatggcttg aatatcacag acggggcatt cctcaaccta 420
 aaaaacctaa gggagttact gcttgaagac aaccagttac ccaaataacc ctctggtttg 480
 ccagagtctt tgacagaact tagtctaatt caaaacaata tataacaat aactaaagag 540
 ggcatttcaa gacttataaa cttgaaaaat ctctatttgg cctggaactg ctattttaac 600
 aaagtttgcg agaaaactaa catagaagat ggagtatttg aaacgctgac aaatttggag 660
 ttgctatcac tatctttcaa ttctctttca cacgtgccac ccaaactgcc aagctcccta 720
 cgcaaacttt ttctgagcaa caccagatc aaatacatta gtgaagaaga tttcaaggga 780
 ttgataaatt taacattact agatttaagc gggaactgtc cgagggtgctt caatgccccca 840
 tttccatgcg tgccttgtga tgggtggtgct tcaattaata tagatcgttt tgcttttcaa 900

58182US002.ST25.txt

aacttgaccc	aacttcgata	cctaaacctc	tctagcactt	ccctcaggaa	gattaatgct	960
gcctgggttta	aaaatatgcc	tcattctgaag	gtgctggatc	ttgaattcaa	ctatttagtg	1020
ggagaaatag	cctctggggc	atttttaacg	atgctgcccc	gcttagaaat	acttgacttg	1080
tcttttaact	atataaagg	gagttatcca	cagcatatta	atatttccag	aaacttctct	1140
aaacttttgt	ctctacgggc	attgcattta	agaggttatg	tgttccagga	actcagagaa	1200
gatgatttcc	agcccctgat	gcagcttcca	aacttatcga	ctatcaactt	gggtattaat	1260
tttattaagc	aaatcgattt	caaacttttc	caaaatttct	ccaatctgga	aattattttac	1320
ttgtcagaaa	acagaatatc	accgttggtta	aaagataccc	ggcagagtta	tgcaaatagt	1380
tcctcttttc	aacgtcatat	ccggaaacga	cgctcaacag	attttgagtt	tgacccacat	1440
tcgaactttt	atcatttcac	ccgtccttta	ataaagccac	aatgtgctgc	ttatggaaaa	1500
gccttagatt	taagcctcaa	cagtattttc	ttcattgggc	caaaccaatt	tgaaaatctt	1560
cctgacattg	cctgttttaa	tctgtctgca	aatagcaatg	ctcaagtgtt	aagtggaaact	1620
gaattttcag	ccattcctca	tgtcaaatat	ttggatttga	caaacaatag	actagacttt	1680
gataatgcta	gtgctcttac	tgaattgtcc	gacttggaag	ttctagatct	cagctataat	1740
tcacactatt	tcagaatagc	aggcgtaaca	catcatctag	aattttattca	aaatttcaca	1800
aatctaaaag	ttttaaaact	gagccacaac	aacattttata	ctttaacaga	taagtataac	1860
ctggaaagca	agtccttggt	agaattagtt	ttcagtggca	atcgccctga	cattttgtgg	1920
aatgatgatg	acaacaggta	tatctccatt	ttcaaaggtc	tcaagaatct	gacacgtctg	1980
gatttatccc	ttaataggct	gaagcacatc	ccaaatgaag	catttccttaa	tttgccagcg	2040
agtctcactg	aactacatat	aaatgataat	atgttaaagt	tttttaactg	gacattactc	2100
cagcagttcc	ctcgtctcga	gttgcttgac	ttacgtggaa	acaaactact	ctttttaact	2160
gatagcctat	ctgactttac	atcttccctt	cggacactgc	tgctgagtca	taacaggatt	2220
tcccacctac	cctctggctt	tctttctgaa	gtcagtagtc	tgaagcacct	cgattttaagt	2280
tccaatctgc	taaaaacaat	caacaaatcc	gcacttgaaa	ctaagaccac	caccaaatta	2340
tctatgttgg	aactacacgg	aaaccctttt	gaatgcacct	gtgacattgg	agatttccga	2400
agatggatgg	atgaacatct	gaatgtcaaa	attcccagac	tggtagatgt	catttgtgcc	2460
agtcctgggg	atcaaagagg	gaagagtatt	gtgagtctgg	agctgacaac	ttgtgtttca	2520
gatgtcactg	cagtgatatt	atttttcttc	acgttcttta	tcaccaccat	ggttatgttg	2580
gctgccctgg	ctcaccattt	gttttactgg	gatgtttggt	ttatatataa	tgtgtgttta	2640
gctaaggtaa	aaggctacag	gtctctttcc	acatcccaaa	ctttctatga	tgcttacatt	2700
tcttatgaca	ccaaagatgc	ctctgttact	gactgggtga	taaatgagct	gcgctaccac	2760

58182US002.ST25.txt

cttgaagaga gccgagacaa aaacgttctc ctttgtctag aggagaggga ttgggacccg 2820
 ggattggcca tcatcgacaa cctcatgcag agcatcaacc aaagcaagaa aacagtattt 2880
 gttttaacca aaaaatatgc aaaaagctgg aactttaaaa cagcttttta cttggctttg 2940
 cagaggctaa tggatgagaa catggatgtg attatatatta tcctgctgga gccagtgtta 3000
 cagcattctc agtatttgag gctacggcag cggatctgta agagctccat cctccagtgg 3060
 cctgacaacc cgaaggcaga aggcttgttt tggcaaacctc tgagaaatgt ggtcttgact 3120
 gaaaatgatt cacggtataa caatatgtat gtcgattcca ttaagcaata ctaactgacg 3180
 ttaagtcatg atttcgcgcc ataataaaga tgcaaaggaa tgacatttct gtattagtta 3240
 tctattgcta tgtaacaaat tatcccaaaa cttagtgggt taaaacaaca catttgctgg 3300
 cccacagttt t 3311

<210> 16
 <211> 1041
 <212> PRT
 <213> Homo sapiens

<400> 16

Met Glu Asn Met Phe Leu Gln Ser Ser Met Leu Thr Cys Ile Phe Leu
1 5 10 15

Leu Ile Ser Gly Ser Cys Glu Leu Cys Ala Glu Glu Asn Phe Ser Arg
20 25 30

Ser Tyr Pro Cys Asp Glu Lys Lys Gln Asn Asp Ser Val Ile Ala Glu
35 40 45

Cys Ser Asn Arg Arg Leu Gln Glu Val Pro Gln Thr Val Gly Lys Tyr
50 55 60

Val Thr Glu Leu Asp Leu Ser Asp Asn Phe Ile Thr His Ile Thr Asn
65 70 75 80

Glu Ser Phe Gln Gly Leu Gln Asn Leu Thr Lys Ile Asn Leu Asn His
85 90 95

Asn Pro Asn Val Gln His Gln Asn Gly Asn Pro Gly Ile Gln Ser Asn
100 105 110

Gly Leu Asn Ile Thr Asp Gly Ala Phe Leu Asn Leu Lys Asn Leu Arg
115 120 125

Glu Leu Leu Leu Glu Asp Asn Gln Leu Pro Gln Ile Pro Ser Gly Leu
130 135 140

58182US002.ST25.txt

Pro Glu Ser Leu Thr Glu Leu Ser Leu Ile Gln Asn Asn Ile Tyr Asn
145 150 155 160

Ile Thr Lys Glu Gly Ile Ser Arg Leu Ile Asn Leu Lys Asn Leu Tyr
165 170 175

Leu Ala Trp Asn Cys Tyr Phe Asn Lys Val Cys Glu Lys Thr Asn Ile
180 185 190

Glu Asp Gly Val Phe Glu Thr Leu Thr Asn Leu Glu Leu Leu Ser Leu
195 200 205

Ser Phe Asn Ser Leu Ser His Val Pro Pro Lys Leu Pro Ser Ser Leu
210 215 220

Arg Lys Leu Phe Leu Ser Asn Thr Gln Ile Lys Tyr Ile Ser Glu Glu
225 230 235 240

Asp Phe Lys Gly Leu Ile Asn Leu Thr Leu Leu Asp Leu Ser Gly Asn
245 250 255

Cys Pro Arg Cys Phe Asn Ala Pro Phe Pro Cys Val Pro Cys Asp Gly
260 265 270

Gly Ala Ser Ile Asn Ile Asp Arg Phe Ala Phe Gln Asn Leu Thr Gln
275 280 285

Leu Arg Tyr Leu Asn Leu Ser Ser Thr Ser Leu Arg Lys Ile Asn Ala
290 295 300

Ala Trp Phe Lys Asn Met Pro His Leu Lys Val Leu Asp Leu Glu Phe
305 310 315 320

Asn Tyr Leu Val Gly Glu Ile Ala Ser Gly Ala Phe Leu Thr Met Leu
325 330 335

Pro Arg Leu Glu Ile Leu Asp Leu Ser Phe Asn Tyr Ile Lys Gly Ser
340 345 350

Tyr Pro Gln His Ile Asn Ile Ser Arg Asn Phe Ser Lys Leu Leu Ser
355 360 365

Leu Arg Ala Leu His Leu Arg Gly Tyr Val Phe Gln Glu Leu Arg Glu
370 375 380

Asp Asp Phe Gln Pro Leu Met Gln Leu Pro Asn Leu Ser Thr Ile Asn
385 390 395 400

58182US002.ST25.txt

Leu Gly Ile Asn Phe Ile Lys Gln Ile Asp Phe Lys Leu Phe Gln Asn
405 410 415

Phe Ser Asn Leu Glu Ile Ile Tyr Leu Ser Glu Asn Arg Ile Ser Pro
420 425 430

Leu Val Lys Asp Thr Arg Gln Ser Tyr Ala Asn Ser Ser Ser Phe Gln
435 440 445

Arg His Ile Arg Lys Arg Arg Ser Thr Asp Phe Glu Phe Asp Pro His
450 455 460

Ser Asn Phe Tyr His Phe Thr Arg Pro Leu Ile Lys Pro Gln Cys Ala
465 470 475 480

Ala Tyr Gly Lys Ala Leu Asp Leu Ser Leu Asn Ser Ile Phe Phe Ile
485 490 495

Gly Pro Asn Gln Phe Glu Asn Leu Pro Asp Ile Ala Cys Leu Asn Leu
500 505 510

Ser Ala Asn Ser Asn Ala Gln Val Leu Ser Gly Thr Glu Phe Ser Ala
515 520 525

Ile Pro His Val Lys Tyr Leu Asp Leu Thr Asn Asn Arg Leu Asp Phe
530 535 540

Asp Asn Ala Ser Ala Leu Thr Glu Leu Ser Asp Leu Glu Val Leu Asp
545 550 555 560

Leu Ser Tyr Asn Ser His Tyr Phe Arg Ile Ala Gly Val Thr His His
565 570 575

Leu Glu Phe Ile Gln Asn Phe Thr Asn Leu Lys Val Leu Asn Leu Ser
580 585 590

His Asn Asn Ile Tyr Thr Leu Thr Asp Lys Tyr Asn Leu Glu Ser Lys
595 600 605

Ser Leu Val Glu Leu Val Phe Ser Gly Asn Arg Leu Asp Ile Leu Trp
610 615 620

Asn Asp Asp Asp Asn Arg Tyr Ile Ser Ile Phe Lys Gly Leu Lys Asn
625 630 635 640

Leu Thr Arg Leu Asp Leu Ser Leu Asn Arg Leu Lys His Ile Pro Asn
Page 39

58182US002.ST25.txt
650

645

655

Glu Ala Phe Leu Asn Leu Pro Ala Ser Leu Thr Glu Leu His Ile Asn
 660 665 670
 Asp Asn Met Leu Lys Phe Phe Asn Trp Thr Leu Leu Gln Gln Phe Pro
 675 680 685
 Arg Leu Glu Leu Leu Asp Leu Arg Gly Asn Lys Leu Leu Phe Leu Thr
 690 695 700
 Asp Ser Leu Ser Asp Phe Thr Ser Ser Leu Arg Thr Leu Leu Leu Ser
 705 710 715 720
 His Asn Arg Ile Ser His Leu Pro Ser Gly Phe Leu Ser Glu Val Ser
 725 730 735
 Ser Leu Lys His Leu Asp Leu Ser Ser Asn Leu Leu Lys Thr Ile Asn
 740 745 750
 Lys Ser Ala Leu Glu Thr Lys Thr Thr Thr Lys Leu Ser Met Leu Glu
 755 760 765
 Leu His Gly Asn Pro Phe Glu Cys Thr Cys Asp Ile Gly Asp Phe Arg
 770 775 780
 Arg Trp Met Asp Glu His Leu Asn Val Lys Ile Pro Arg Leu Val Asp
 785 790 795 800
 Val Ile Cys Ala Ser Pro Gly Asp Gln Arg Gly Lys Ser Ile Val Ser
 805 810 815
 Leu Glu Leu Thr Thr Cys Val Ser Asp Val Thr Ala Val Ile Leu Phe
 820 825 830
 Phe Phe Thr Phe Phe Ile Thr Thr Met Val Met Leu Ala Ala Leu Ala
 835 840 845
 His His Leu Phe Tyr Trp Asp Val Trp Phe Ile Tyr Asn Val Cys Leu
 850 855 860
 Ala Lys Val Lys Gly Tyr Arg Ser Leu Ser Thr Ser Gln Thr Phe Tyr
 865 870 875 880
 Asp Ala Tyr Ile Ser Tyr Asp Thr Lys Asp Ala Ser Val Thr Asp Trp
 885 890 895

58182US002.ST25.txt

Val Ile Asn Glu Leu Arg Tyr His Leu Glu Glu Ser Arg Asp Lys Asn
 900 905 910

Val Leu Leu Cys Leu Glu Glu Arg Asp Trp Asp Pro Gly Leu Ala Ile
 915 920 925

Ile Asp Asn Leu Met Gln Ser Ile Asn Gln Ser Lys Lys Thr Val Phe
 930 935 940

Val Leu Thr Lys Lys Tyr Ala Lys Ser Trp Asn Phe Lys Thr Ala Phe
 945 950 955 960

Tyr Leu Ala Leu Gln Arg Leu Met Asp Glu Asn Met Asp Val Ile Ile
 965 970 975

Phe Ile Leu Leu Glu Pro Val Leu Gln His Ser Gln Tyr Leu Arg Leu
 980 985 990

Arg Gln Arg Ile Cys Lys Ser Ser Ile Leu Gln Trp Pro Asp Asn Pro
 995 1000 1005

Lys Ala Glu Gly Leu Phe Trp Gln Thr Leu Arg Asn Val Val Leu
 1010 1015 1020

Thr Glu Asn Asp Ser Arg Tyr Asn Asn Met Tyr Val Asp Ser Ile
 1025 1030 1035

Lys Gln Tyr
 1040

<210> 17
 <211> 3352
 <212> DNA
 <213> Homo sapiens

<400> 17
 aggctggtat aaaaatctta cttcctctat tctctgagcc gctgctgccc ctgtgggaag 60
 ggacctcgag tgtgaagcat ccttcctgt agctgctgtc cagtctgccc gccagaccct 120
 ctggagaagc cctgcccc cagcatgggt ttctgccgca gcgccctgca cccgctgtct 180
 ctcctggtgc aggccatcat gctggccatg accctggccc tgggtacctt gcctgccttc 240
 ctaccctgtg agctccagcc ccacggcctg gtgaactgca actggctgtt cctgaagtct 300
 gtgccccact tctccatggc agcaccccggt ggcaatgtca ccagcctttc cttgtcctcc 360
 aaccgcatcc accacctcca tgattctgac ttgcccacc tgcccagcct gcggcatctc 420
 aacctcaagt ggaactgccc gccggttggc ctcagcccca tgcacttccc ctgccacatg 480
 accatcgagc ccagcacctt cttggctgtg cccaccctgg aagagctaaa cctgagctac 540

58182US002.ST25.txt

aacaacatca tgactgtgcc tgcgctgccc aaatccctca tatccctgtc cctcagccat 600
accaacatcc tgatgctaga ctctgccagc ctcgccggcc tgcattgccct gcgcttccta 660
ttcatggacg gcaactgtta ttacaagaac ccctgcaggc aggacttga ggtggccccg 720
ggtgccctcc ttggcctggg caacctcacc cacctgtcac tcaagtacaa caacctcact 780
gtggtgcccc gcaacctgcc ttccagcctg gagtatctgc tgttgctcta caaccgcatc 840
gtcaaactgg cgcctgagga cctggccaat ctgaccgccc tgcgtgtgct cgatgtgggc 900
ggaaattgcc gccgctgcga ccacgctccc aaccttgca tggagtggcc tcgtcacttc 960
ccccagctac atcccgatac cttcagccac ctgagccgtc ttgaaggcct ggtgttgaag 1020
gacagttctc tctcctggct gaatgccagt tggttccgtg ggctgggaaa cctccgagtg 1080
ctggacctga gtgagaactt cctctacaaa tgcatacta aaaccaaggc cttccagggc 1140
ctaacacagc tgcgcaagct taacctgtcc ttcaattacc aaaagagggt gtcctttgcc 1200
cacctgtctc tggccccttc cttcgggagc ctggctgccc tgaaggagct ggacatgcac 1260
ggcatcttct tccgctcact cgatgagacc acgctccggc cactggcccc cctgccccatg 1320
ctccagactc tgcgtctgca gatgaacttc atcaaccagg cccagctcgg catcttcagg 1380
gccttccttg gcctgcgcta cgtggacctg tcggacaacc gcatcagcgg agcttcggag 1440
ctgacagcca ccatggggga ggcagatgga ggggagaagg tctggctgca gcctggggac 1500
cttgctccgg cccagtgga cactcccagc tctgaagact tcaggcccaa ctgcagcacc 1560
ctcaacttca ccttgatct gtcacggaac aacctggtga ccgtgcagcc ggagatgttt 1620
gcccagctct cgcacctgca gtgcctgctc ctgagccaca actgcatctc gcaggcagtc 1680
aatggctccc agttcctgcc gctgaccggt ctgcaggtgc tagacctgtc ccgcaataag 1740
ctggacctct accacgagca ctcatcacg gagctaccgc gactggaggc cctggacctc 1800
agctacaaca gccagccctt tggcatgcag ggcgtgggccc acaacttcag cttcgtggct 1860
cacctgcgca ccctgcgcca cctcagcctg gcccacaaca acatccacag ccaagtgtcc 1920
cagcagctct gcagtacgtc gctgcggggc ctggacttca gcggcaatgc actggggccat 1980
atgtggggccg agggagacct ctatctgcac ttcttccaag gcctgagcgg tttgatctgg 2040
ctggacttgt cccagaaccg cctgcacacc ctctgcccc aaacctgctg caacctcccc 2100
aagagcctac aggtgctgct tctccgtgac aattacctgg ctttctttaa gtggtggagc 2160
ctccacttcc tgcccaaact ggaagtcctc gacctggcag gaaaccggct gaaggccctg 2220
accaatggca gcctgcctgc tggcaccggt ctccggaggc tggatgtcag ctgcaacagc 2280
atcagcttcg tggcccccg cttcttttcc aaggccaagg agctgcgaga gctcaacctt 2340
agcgccaacg ccctcaagac agtggaccac tcctggtttg ggcccctggc gagtgccctg 2400

58182US002.ST25.txt

```

caaatactag atgtaagcgc caaccctctg cactgcgccct gtggggcggc ctttatggac 2460
ttcctgctgg aggtgcaggc tgccgtgccc ggtctgcca gccgggtgaa gtgtggcagt 2520
ccgggccagc tccagggcct cagcatcttt gcacaggacc tgcgcctctg cctggatgag 2580
gccctctcct gggactgttt cgccctctcg ctgctggctg tggctctggg cctgggtgtg 2640
cccatgctgc atcacctctg tggctgggac ctctggtact gcttccacct gtgcctggcc 2700
tggcttcctt ggcgggggcg gcaaagtggg cgagatgagg atgccctgcc ctacgatgcc 2760
ttcgtggtct tcgacaaaac gcagagcgca gtggcagact ggggtgtacaa cgagcttcgg 2820
gggcagctgg aggagtgccg tgggcgctgg gcactccgcc tgtgcctgga ggaacgcgac 2880
tggctgcctg gcaaaaccct ctttgagaac ctgtgggcct cggctctatgg cagccgcaag 2940
acgctgtttg tgctggccca cacggaccgg gtcagtggtc tcttgcgcg cagcttcctg 3000
ctggcccagc agcgcttgct ggaggaccgc aaggacgtcg tggtgctggt gatcctgagc 3060
cctgacggcc gccgctcccg ctacgtgcgg ctgcgccagc gcctctgccg ccagagtgtc 3120
ctcctctggc ccaccagcc cagtggtcag cgcagcttct gggcccagct gggcatggcc 3180
ctgaccaggg acaaccacca cttctataac cggaacttct gccagggacc cacggccgaa 3240
tagccgtgag ccggaatcct gcacggtgcc acctccacac tcacctacc tctgcctgcc 3300
tggcttgacc ctcccctgct cgctccctc accccacacc tgacacagag ca 3352

```

<210> 18
 <211> 1032
 <212> PRT
 <213> Homo sapiens

<400> 18

Met Gly Phe Cys Arg Ser Ala Leu His Pro Leu Ser Leu Leu Val Gln
 1 5 10 15

Ala Ile Met Leu Ala Met Thr Leu Ala Leu Gly Thr Leu Pro Ala Phe
 20 25 30

Leu Pro Cys Glu Leu Gln Pro His Gly Leu Val Asn Cys Asn Trp Leu
 35 40 45

Phe Leu Lys Ser Val Pro His Phe Ser Met Ala Ala Pro Arg Gly Asn
 50 55 60

Val Thr Ser Leu Ser Leu Ser Ser Asn Arg Ile His His Leu His Asp
 65 70 75 80

Ser Asp Phe Ala His Leu Pro Ser Leu Arg His Leu Asn Leu Lys Trp
 85 90 95

58182US002.ST25.txt

Asn Cys Pro Pro Val Gly Leu Ser Pro Met His Phe Pro Cys His Met
 100 105 110
 Thr Ile Glu Pro Ser Thr Phe Leu Ala Val Pro Thr Leu Glu Glu Leu
 115 120 125
 Asn Leu Ser Tyr Asn Asn Ile Met Thr Val Pro Ala Leu Pro Lys Ser
 130 135 140
 Leu Ile Ser Leu Ser Leu Ser His Thr Asn Ile Leu Met Leu Asp Ser
 145 150 155 160
 Ala Ser Leu Ala Gly Leu His Ala Leu Arg Phe Leu Phe Met Asp Gly
 165 170 175
 Asn Cys Tyr Tyr Lys Asn Pro Cys Arg Gln Ala Leu Glu Val Ala Pro
 180 185 190
 Gly Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr
 195 200 205
 Asn Asn Leu Thr Val Val Pro Arg Asn Leu Pro Ser Ser Leu Glu Tyr
 210 215 220
 Leu Leu Leu Ser Tyr Asn Arg Ile Val Lys Leu Ala Pro Glu Asp Leu
 225 230 235 240
 Ala Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg
 245 250 255
 Arg Cys Asp His Ala Pro Asn Pro Cys Met Glu Cys Pro Arg His Phe
 260 265 270
 Pro Gln Leu His Pro Asp Thr Phe Ser His Leu Ser Arg Leu Glu Gly
 275 280 285
 Leu Val Leu Lys Asp Ser Ser Leu Ser Trp Leu Asn Ala Ser Trp Phe
 290 295 300
 Arg Gly Leu Gly Asn Leu Arg Val Leu Asp Leu Ser Glu Asn Phe Leu
 305 310 315 320
 Tyr Lys Cys Ile Thr Lys Thr Lys Ala Phe Gln Gly Leu Thr Gln Leu
 325 330 335
 Arg Lys Leu Asn Leu Ser Phe Asn Tyr Gln Lys Arg Val Ser Phe Ala
 340 345 350

58182US002.ST25.txt

His Leu Ser Leu Ala Pro Ser Phe Gly Ser Leu Val Ala Leu Lys Glu
355 360 365

Leu Asp Met His Gly Ile Phe Phe Arg Ser Leu Asp Glu Thr Thr Leu
370 375 380

Arg Pro Leu Ala Arg Leu Pro Met Leu Gln Thr Leu Arg Leu Gln Met
385 390 395 400

Asn Phe Ile Asn Gln Ala Gln Leu Gly Ile Phe Arg Ala Phe Pro Gly
405 410 415

Leu Arg Tyr Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Ser Glu
420 425 430

Leu Thr Ala Thr Met Gly Glu Ala Asp Gly Gly Glu Lys Val Trp Leu
435 440 445

Gln Pro Gly Asp Leu Ala Pro Ala Pro Val Asp Thr Pro Ser Ser Glu
450 455 460

Asp Phe Arg Pro Asn Cys Ser Thr Leu Asn Phe Thr Leu Asp Leu Ser
465 470 475 480

Arg Asn Asn Leu Val Thr Val Gln Pro Glu Met Phe Ala Gln Leu Ser
485 490 495

His Leu Gln Cys Leu Arg Leu Ser His Asn Cys Ile Ser Gln Ala Val
500 505 510

Asn Gly Ser Gln Phe Leu Pro Leu Thr Gly Leu Gln Val Leu Asp Leu
515 520 525

Ser Arg Asn Lys Leu Asp Leu Tyr His Glu His Ser Phe Thr Glu Leu
530 535 540

Pro Arg Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Gly
545 550 555 560

Met Gln Gly Val Gly His Asn Phe Ser Phe Val Ala His Leu Arg Thr
565 570 575

Leu Arg His Leu Ser Leu Ala His Asn Asn Ile His Ser Gln Val Ser
580 585 590

Gln Gln Leu Cys Ser Thr Ser Leu Arg Ala Leu Asp Phe Ser Gly Asn
Page 45

58182US002.ST25.txt
595 600 605

Ala Leu Gly His Met Trp Ala Glu Gly Asp Leu Tyr Leu His Phe Phe
610 615 620

Gln Gly Leu Ser Gly Leu Ile Trp Leu Asp Leu Ser Gln Asn Arg Leu
625 630 635 640

His Thr Leu Leu Pro Gln Thr Leu Arg Asn Leu Pro Lys Ser Leu Gln
645 650 655

Val Leu Arg Leu Arg Asp Asn Tyr Leu Ala Phe Phe Lys Trp Trp Ser
660 665 670

Leu His Phe Leu Pro Lys Leu Glu Val Leu Asp Leu Ala Gly Asn Arg
675 680 685

Leu Lys Ala Leu Thr Asn Gly Ser Leu Pro Ala Gly Thr Arg Leu Arg
690 695 700

Arg Leu Asp Val Ser Cys Asn Ser Ile Ser Phe Val Ala Pro Gly Phe
705 710 715 720

Phe Ser Lys Ala Lys Glu Leu Arg Glu Leu Asn Leu Ser Ala Asn Ala
725 730 735

Leu Lys Thr Val Asp His Ser Trp Phe Gly Pro Leu Ala Ser Ala Leu
740 745 750

Gln Ile Leu Asp Val Ser Ala Asn Pro Leu His Cys Ala Cys Gly Ala
755 760 765

Ala Phe Met Asp Phe Leu Leu Glu Val Gln Ala Ala Val Pro Gly Leu
770 775 780

Pro Ser Arg Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly Leu Ser
785 790 795 800

Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Ala Leu Ser Trp
805 810 815

Asp Cys Phe Ala Leu Ser Leu Leu Ala Val Ala Leu Gly Leu Gly Val
820 825 830

Pro Met Leu His His Leu Cys Gly Trp Asp Leu Trp Tyr Cys Phe His
835 840 845

58182US002.ST25.txt

Leu Cys Leu Ala Trp Leu Pro Trp Arg Gly Arg Gln Ser Gly Arg Asp
850 855 860

Glu Asp Ala Leu Pro Tyr Asp Ala Phe Val Val Phe Asp Lys Thr Gln
865 870 875 880

Ser Ala Val Ala Asp Trp Val Tyr Asn Glu Leu Arg Gly Gln Leu Glu
885 890 895

Glu Cys Arg Gly Arg Trp Ala Leu Arg Leu Cys Leu Glu Glu Arg Asp
900 905 910

Trp Leu Pro Gly Lys Thr Leu Phe Glu Asn Leu Trp Ala Ser Val Tyr
915 920 925

Gly Ser Arg Lys Thr Leu Phe Val Leu Ala His Thr Asp Arg Val Ser
930 935 940

Gly Leu Leu Arg Ala Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu
945 950 955 960

Asp Arg Lys Asp Val Val Val Leu Val Ile Leu Ser Pro Asp Gly Arg
965 970 975

Arg Ser Arg Tyr Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val
980 985 990

Leu Leu Trp Pro His Gln Pro Ser Gly Gln Arg Ser Phe Trp Ala Gln
995 1000 1005

Leu Gly Met Ala Leu Thr Arg Asp Asn His His Phe Tyr Asn Arg
1010 1015 1020

Asn Phe Cys Gln Gly Pro Thr Ala Glu
1025 1030

<210> 19
<211> 3002
<212> DNA
<213> Homo sapiens

<400> 19
gtggcttggt attcactggc aggtttcaga catttagatc tttcttttaa tgactaacac 60
catgcctatc tgtggagaag ctggcaacat gtcacacctg gaaattgttt ttcaacatta 120
atactattat ttggcagtaa tccagattgc ttttgccacc aacctgaaga catatagagg 180
cagaaggaca ggaataattc tatttgtttc ctgttttgaa acttccatct gtaaggctat 240
caaaaggaga tgtgagagag ggtattgagt ctggcctgac aatgcagttc ttaaaccaaa 300

58182US002.ST25.txt

ggtccattat gcttctcctc tctgagaatc ctgacttacc tcaacaacgg agacatggca	360
cagtagccag cttggagact tctcagccaa tgctctgaga tcaagtcgaa gaccaaatat	420
acagggtttt gagctcatct tcatcattca tatgaggaaa taagtggtaa aatccttgga	480
aatacaatga gactcatcag aaacattttac atatttttgta gtattgttat gacagcagag	540
ggtgatgctc cagagctgcc agaagaaagg gaactgatga ccaactgctc caacatgtct	600
ctaagaaagg ttcccgcaga cttgacccca gccacaacga cactggattt atcctataac	660
ctcctttttc aactccagag ttcagatttt cattctgtct ccaaactgag agttttgatt	720
ctatgccata acagaattca acagctggat ctcaaaacct ttgaattcaa caaggagtta	780
agatatttag atttgtctaa taacagactg aagagtgtaa cttggtattt actggcaggt	840
ctcaggtatt tagatctttc ttttaatgac ttgacacca tgcctatctg tgaggaagct	900
ggcaacatgt cacacctgga aatcctaggt ttgagtgggg caaaaataca aaaatcagat	960
ttccagaaaa ttgctcatct gcatctaaat actgtcttct taggattcag aactcttcct	1020
cattatgaag aaggtagcct gcccatctta aacacaacaa aactgcacat tgttttacca	1080
atggacacaa atttctgggt tcttttgctg gatggaatca agacttcaaa aatattagaa	1140
atgacaaata tagatggcaa aagccaattt gtaagttagt aaatgcaacg aaatcttagt	1200
ttagaaaatg ctaagacatc ggttctattg cttaataaag ttgatttact ctgggacgac	1260
cttttcctta tcttacaatt tgtttgcat acatcagtg aacactttca gatccgaaat	1320
gtgacttttg gtggttaaggc ttatcttgac cacaattcat ttgactactc aaatactgta	1380
atgagaacta taaaattgga gcatgtacat ttcagagtgt ttacattca acaggataaa	1440
atctatttgc ttttgaccaa aatggacata gaaaacctga caatatcaaa tgcacaaatg	1500
ccacacatgc ttttcccgaa ttatcctacg aaattccaat atttaaattt tgccaataat	1560
atcttaacag acgagttggt taaaagaact atccaactgc ctcaattgaa aactctcatt	1620
ttgaatggca ataaactgga gacactttct ttagtaagtt gctttgctaa caacacaccc	1680
ttggaacact tggatctgag tcaaaatcta ttacaacata aaaatgatga aaattgctca	1740
tggccagaaa ctgtggtcaa tatgaatctg tcatacaata aattgtctga ttctgtcttc	1800
aggtgcttgc ccaaagtat tcaaatactt gacctaaata ataaccaaat ccaaactgta	1860
cctaaagaga ctattcatct gatggcctta cgagaactaa atattgcatt taattttcta	1920
actgatctcc ctggatgcag tcatttcagt agactttcag ttctgaacat tgaaatgaac	1980
ttcattctca gccatctct ggattttgtt cagagctgcc aggaagttaa aactctaaat	2040
gcgggaagaa atccattccg gtgtacctgt gaattaaaaa atttcattca gcttgaaaca	2100
tattcagagg tcatgatggt tggatggtca gattcataca cctgtgaata ccctttaaac	2160

58182US002.ST25.txt

```

ctaaggggaa ttaggttaaa agacgttcat ctccacgaat tatcttgcaa cacagctctg 2220
ttgattgtca ccattgtggt tattatgcta gttctgggggt tggctgtggc cttctgctgt 2280
ctccactttg atctgccctg gtatctcagg atgctaggtc aatgcacaca aacatggcac 2340
agggttagga aaacaaccca agaacaactc aagagaaatg tccgattcca cgcatttatt 2400
tcatacagtg aacatgattc tctgtgggtg aagaatgaat tgatcccca tctagagaag 2460
gaagatgggt ctatcttgat ttgcctttat gaaagctact ttgaccctgg caaaagcatt 2520
agtgaaaata ttgtaagctt cattgagaaa agctataagt ccatctttgt tttgtctccc 2580
aactttgtcc agaatgagt gtgccattat gaattttact ttgccacca caatctcttc 2640
catgaaaatt ctgatcatat aattcttata ttactggaac ccattccatt ctattgcatt 2700
cccaccaggt atcataaact gaaagctctc ctggaaaaaa aagcatactt ggaatggccc 2760
aaggataggc gtaaattgtg gcttttctgg gcaaaccctc gagctgctat taatgttaat 2820
gtattagcca ccagagaaat gtatgaactg cagacattca cagagttaaa tgaagagtct 2880
cgaggttcta caatctctct gatgagaaca gattgtctat aaaatcccac agtccttggg 2940
aagttgggga ccacatacac tgttgggatg tacattgata caacctttat gatggcaatt 3000
tg 3002

```

<210> 20
 <211> 811
 <212> PRT
 <213> Homo sapiens

<400> 20

Met Arg Leu Ile Arg Asn Ile Tyr Ile Phe Cys Ser Ile Val Met Thr
 1 5 10 15

Ala Glu Gly Asp Ala Pro Glu Leu Pro Glu Glu Arg Glu Leu Met Thr
 20 25 30

Asn Cys Ser Asn Met Ser Leu Arg Lys Val Pro Ala Asp Leu Thr Pro
 35 40 45

Ala Thr Thr Thr Leu Asp Leu Ser Tyr Asn Leu Leu Phe Gln Leu Gln
 50 55 60

Ser Ser Asp Phe His Ser Val Ser Lys Leu Arg Val Leu Ile Leu Cys
 65 70 75 80

His Asn Arg Ile Gln Gln Leu Asp Leu Lys Thr Phe Glu Phe Asn Lys
 85 90 95

Glu Leu Arg Tyr Leu Asp Leu Ser Asn Asn Arg Leu Lys Ser Val Thr
 Page 49

58182US002.ST25.txt

100

105

110

Trp Tyr Leu Leu Ala Gly Leu Arg Tyr Leu Asp Leu Ser Phe Asn Asp
115 120 125

Phe Asp Thr Met Pro Ile Cys Glu Glu Ala Gly Asn Met Ser His Leu
130 135 140

Glu Ile Leu Gly Leu Ser Gly Ala Lys Ile Gln Lys Ser Asp Phe Gln
145 150 155 160

Lys Ile Ala His Leu His Leu Asn Thr Val Phe Leu Gly Phe Arg Thr
165 170 175

Leu Pro His Tyr Glu Glu Gly Ser Leu Pro Ile Leu Asn Thr Thr Lys
180 185 190

Leu His Ile Val Leu Pro Met Asp Thr Asn Phe Trp Val Leu Leu Arg
195 200 205

Asp Gly Ile Lys Thr Ser Lys Ile Leu Glu Met Thr Asn Ile Asp Gly
210 215 220

Lys Ser Gln Phe Val Ser Tyr Glu Met Gln Arg Asn Leu Ser Leu Glu
225 230 235 240

Asn Ala Lys Thr Ser Val Leu Leu Leu Asn Lys Val Asp Leu Leu Trp
245 250 255

Asp Asp Leu Phe Leu Ile Leu Gln Phe Val Trp His Thr Ser Val Glu
260 265 270

His Phe Gln Ile Arg Asn Val Thr Phe Gly Gly Lys Ala Tyr Leu Asp
275 280 285

His Asn Ser Phe Asp Tyr Ser Asn Thr Val Met Arg Thr Ile Lys Leu
290 295 300

Glu His Val His Phe Arg Val Phe Tyr Ile Gln Gln Asp Lys Ile Tyr
305 310 315 320

Leu Leu Leu Thr Lys Met Asp Ile Glu Asn Leu Thr Ile Ser Asn Ala
325 330 335

Gln Met Pro His Met Leu Phe Pro Asn Tyr Pro Thr Lys Phe Gln Tyr
340 345 350

58182US002.ST25.txt
Leu Asn Phe Ala Asn Asn Ile Leu Thr Asp Glu Leu Phe Lys Arg Thr
355 360 365
Ile Gln Leu Pro His Leu Lys Thr Leu Ile Leu Asn Gly Asn Lys Leu
370 375 380
Glu Thr Leu Ser Leu Val Ser Cys Phe Ala Asn Asn Thr Pro Leu Glu
385 390 395 400
His Leu Asp Leu Ser Gln Asn Leu Leu Gln His Lys Asn Asp Glu Asn
405 410 415
Cys Ser Trp Pro Glu Thr Val Val Asn Met Asn Leu Ser Tyr Asn Lys
420 425 430
Leu Ser Asp Ser Val Phe Arg Cys Leu Pro Lys Ser Ile Gln Ile Leu
435 440 445
Asp Leu Asn Asn Asn Gln Ile Gln Thr Val Pro Lys Glu Thr Ile His
450 455 460
Leu Met Ala Leu Arg Glu Leu Asn Ile Ala Phe Asn Phe Leu Thr Asp
465 470 475 480
Leu Pro Gly Cys Ser His Phe Ser Arg Leu Ser Val Leu Asn Ile Glu
485 490 495
Met Asn Phe Ile Leu Ser Pro Ser Leu Asp Phe Val Gln Ser Cys Gln
500 505 510
Glu Val Lys Thr Leu Asn Ala Gly Arg Asn Pro Phe Arg Cys Thr Cys
515 520 525
Glu Leu Lys Asn Phe Ile Gln Leu Glu Thr Tyr Ser Glu Val Met Met
530 535 540
Val Gly Trp Ser Asp Ser Tyr Thr Cys Glu Tyr Pro Leu Asn Leu Arg
545 550 555 560
Gly Ile Arg Leu Lys Asp Val His Leu His Glu Leu Ser Cys Asn Thr
565 570 575
Ala Leu Leu Ile Val Thr Ile Val Val Ile Met Leu Val Leu Gly Leu
580 585 590
Ala Val Ala Phe Cys Cys Leu His Phe Asp Leu Pro Trp Tyr Leu Arg
595 600 605

58182US002.ST25.txt

Met Leu Gly Gln Cys Thr Gln Thr Trp His Arg Val Arg Lys Thr Thr
610 615 620

Gln Glu Gln Leu Lys Arg Asn Val Arg Phe His Ala Phe Ile Ser Tyr
625 630 635 640

Ser Glu His Asp Ser Leu Trp Val Lys Asn Glu Leu Ile Pro Asn Leu
645 650 655

Glu Lys Glu Asp Gly Ser Ile Leu Ile Cys Leu Tyr Glu Ser Tyr Phe
660 665 670

Asp Pro Gly Lys Ser Ile Ser Glu Asn Ile Val Ser Phe Ile Glu Lys
675 680 685

Ser Tyr Lys Ser Ile Phe Val Leu Ser Pro Asn Phe Val Gln Asn Glu
690 695 700

Trp Cys His Tyr Glu Phe Tyr Phe Ala His His Asn Leu Phe His Glu
705 710 715 720

Asn Ser Asp His Ile Ile Leu Ile Leu Leu Glu Pro Ile Pro Phe Tyr
725 730 735

Cys Ile Pro Thr Arg Tyr His Lys Leu Lys Ala Leu Leu Glu Lys Lys
740 745 750

Ala Tyr Leu Glu Trp Pro Lys Asp Arg Arg Lys Cys Gly Leu Phe Trp
755 760 765

Ala Asn Leu Arg Ala Ala Ile Asn Val Asn Val Leu Ala Thr Arg Glu
770 775 780

Met Tyr Glu Leu Gln Thr Phe Thr Glu Leu Asn Glu Glu Ser Arg Gly
785 790 795 800

Ser Thr Ile Ser Leu Met Arg Thr Asp Cys Leu
805 810

<210> 21

<211> 215

<212> DNA

<213> Homo sapiens

<400> 21

aaaaacaaaa catttgagaa acacggctct aaactcatgt aaagagtgca tgaaggaaag 60

caaaaacaga aatggaaagt ggcccagaag cattaagaaa gtggaaatca gtatgttccc 120

58182US002.ST25.txt
tattttaaggc atttgcagga agcaaggcct tcagagaacc tagagcccaa ggttcagagt 180
cacccatctc agcaagccca gaagtatctg caata 215

<210> 22
<211> 36
<212> DNA
<213> Artificial

<220>
<223> 5' primer for human IFN-alpha promoter

<400> 22
acgagatcta agcttaaaac aaaacatttg agaaac 36

<210> 23
<211> 28
<212> DNA
<213> Artificial

<220>
<223> 3' primer for human IFN-alpha promoter

<400> 23
acgagatcta gatattgcag atacttct 28